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THE LIVER IN HEART FAILURE

RELATION OF ANATOMICAL, FUNCTIONAL, AND CIRCULATORY CHANGES

BY

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A congested " nutmeg " liver is a common post-mortem finding in patients dying from heart failure and the microscopic description dates from Kiernan (1833). Similarly, it is known that biochemical tests of liver function are abnormal in circulatory failure (Jolliffe, 1930; Bernstein, Le Winn and Simkins, 1942; Chávez, Sepúlveda and Ortega, 1943). However, the correlation of functional changes with the hepatic histology has not been attempted in a series of any magnitude, and the evolution of liver changes from mild to severe heart failure requires elucidation. Aspiration liver biopsy and various biochemical tests have been utilized in this attempt to clarify some of the outstanding problems. In many instances hæmodynamic data were available from cardiac catheter studies.

METHODS

Liver tissue was obtained by a modification (Sherlock, 1945) of the aspiration liver biopsy technique of Iversen and Roholm (1939). Hæmorrhage might be anticipated from puncture of the " congested " liver of heart failure, but the 41 biopsies performed were uncomplicated and well tolerated. Necropsy material is of limited value owing to rapid autolysis, as will be described later. It was never used to evaluate cellular changes, but liver puncture material taken within two hours of death was occasionally used to assess fibrosis.

Material fixed in 10 per cent formol-saline was stained with hæmatoxylin and eosin, with a modified silver impregnation method for reticulin and with Mallory's picric stain for connective tissue. The presence of fat was checked by Sudan III frozen sections. Faint staining with methylene blue showed up bile pigment. Iron was demonstrated by the Prussian blue method, and glycogen by Best's carmine stain on alcohol fixed tissue.

A full post-mortem examination was carried out in 28 patients, particular attention being paid to the colour of the bile and the state of the bile passages, ascites, infarction in the organs, the size of the spleen, and the possibility of a portal collateral circulation.

Biochemical methods. Serum was analysed for bilirubin by the method of Haslewood and King (1937), for alkaline phosphatase by the method of King and Armstrong (1934), and for proteins, King *et al.* (1937, 1942). The technique of Maclagan (1944) was used for the colloidal gold reaction. The bromsulphalein test using 5 mg./kg. body weight was employed according to Helm and Machella (1942). Urine urobilinogen was determined qualitatively by Erhlich's reagent, and quantitatively on 24-hour samples by the method of Watson (1937). Schlesinger's test was used for urobilin. The methylene blue method of Gellis and Stokes (1945) and diazo tests of Pollock (1945) were employed for urine bilirubin determinations. Normal values for these methods are shown in Tables II and IV.

Circulatory studies. Cardiac output (CO) and right auricular pressure (RAP) were estimated by the technique described by McMichael and Sharpey-Schafer (1944). Arterial oxygen saturation was sometimes measured.

As all these investigations could not be performed on the same day, the cardiac catheterization and the biochemical studies were done together and the liver biopsy within three days of these.

Clinical Material

It was inevitable that some selection of patients should occur, the association of visible icterus and heart failure prompting investigation. To balance this, patients in heart failure, not obviously jaundiced, were also included. Fifty-one patients were studied with all the common ætiological varieties of acquired heart disease. Apart from one patient with constrictive pericarditis the fifty other patients were all in congestive heart failure as judged by increased jugular venous pressure, presence of crepitations at the lung bases, tenderness of the liver, and peripheral œdema.

The extent of centrilobular hepatic necrosis was graded as follows.

(A) The hepatocellular changes confined to the region immediately adjoining the centrilobular hepatic vein (18 patients).

(B) Liver cell necrosis extended from the central vein one-third the distance towards the periphery of the lobule (15 patients).

(C) Disappearance of liver cells over an area greater than the inner third of the lobules (17 patients).

The two more severe grades are illustrated in Fig. 1 and 2. To avoid bias the grading was done by one observer without clinical or other data.

General Description of the Liver in Heart Failure

Liver weights were variable and bore no relation to the clinical assessment of hepatic size. This might be due to drainage of blood post mortem from an over-distended liver. The disparity between the finding at necropsy of a liver of normal weight, and the clinical signs during life of hepatic enlargement, was perhaps explicable on this basis.

Hepatic histology. The general anatomy of the lobule was usually intact, the portal tracts bearing their normal relationship to the central hepatic vein (Fig. 2). Sometimes the lobular pattern was reversed, the portal tracts apparently lying centrally with a ring of surrounding fibrous tissue passing from central vein to central vein. This was characteristic of cardiac cirrhosis.

The central vein was always dilated and the sinusoids entering it were engorged for a variable distance towards the periphery of the lobule. In severe cases there was frank hæmorrhage from the sinusoids (Fig. 1 and 10). There was usually some disappearance of liver cells. The remaining liver cells showed a variety of degenerative changes. The cytoplasm was shrunken with excessive granularity. The nuclei showed fragmentation and pyknosis, these changes diminishing in intensity as the portal zones were reached (Fig. 2). Apart from cardiac cirrhosis the portal tracts were essentially normal (Fig. 2 and 5). Each portal tract was surrounded by relatively normal liver cells to a depth that varied inversely with the central necrosis.

Diffuse loss of liver glycogen was noted only in the agonal stages. Surviving cells usually contained their normal complement of glycogen. This was true not only of the relatively normal portal zone but also of the surviving liver cells lying amidst the debris at the centre of the lobule. Biopsy sections showed significant fatty change in only 15 of the 41 available sections. The fat was in scattered droplets (Fig. 10); only rarely was there distension of the liver cell by one large globule. Sometimes the fatty change was peripheral (8 cases), occasionally central (3 cases) or diffusely scattered through the lobule (4 cases). This contrasted completely with the usual post-mortem picture.

Increased brown pigment in the liver cells at the centre of the lobule was constant. In many instances large pigment granules filled the central degenerating cells. As the cells disintegrated the pigment came to lie free at the centre of the lobule amidst cellular debris. This brown pigment failed to give the Prussian blue reaction and was also negative to tests for hæmofuscin. Sudan III stained the granules a rich brown, both in frozen and formol fixed sections. The pigment stained green with methylene blue suggesting a relationship to bile pigment.

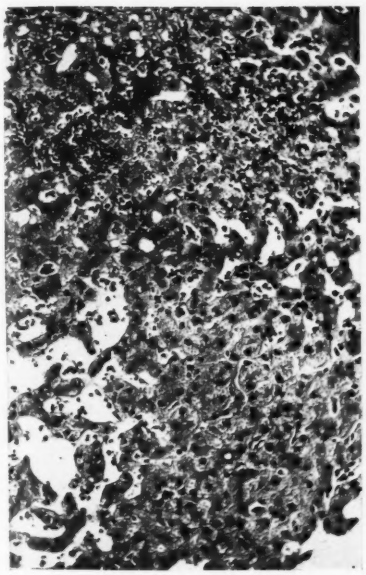

FIG. 1.—Grade B. Ischæmic heart failure. Serum bilirubin, 2·1 mg./100 ml.; RAP, +27 cm. saline; CO_2 4·5 l./minute. Liver cells have disappeared from the centre of the lobule and are replaced by frank hæmorrhage. Liver cells peripherally show some degenerative changes and "glycogenic" infiltration in their nuclei is conspicuous. H. and (E. ×120).

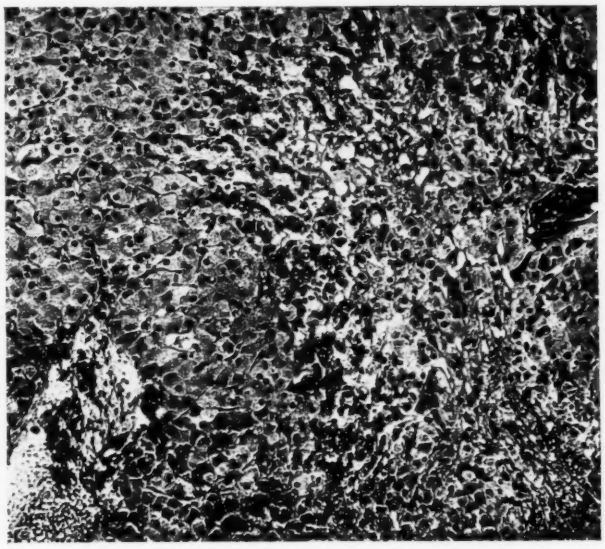

FIG. 2.—Grade C. Case 5. Cor pulmonale; two hours before death. Serum bilirubin, 3·4 mg./100 ml.; RAP, +16 cm. saline; CO_2 3·5 l./minute and arterial oxygen saturation 59 per cent. Gross centrilobular congestion and liver cell necrosis. Pigment increase is seen in the degenerating liver cells. Liver cells at the periphery of the lobule are relatively normal. H.E. (×120).

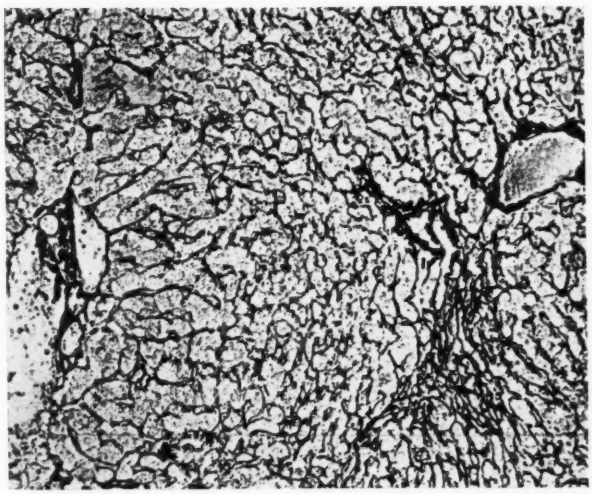

FIG. 3.—Case 5. Reticulin stains show condensation at the lobular centre. (×120).

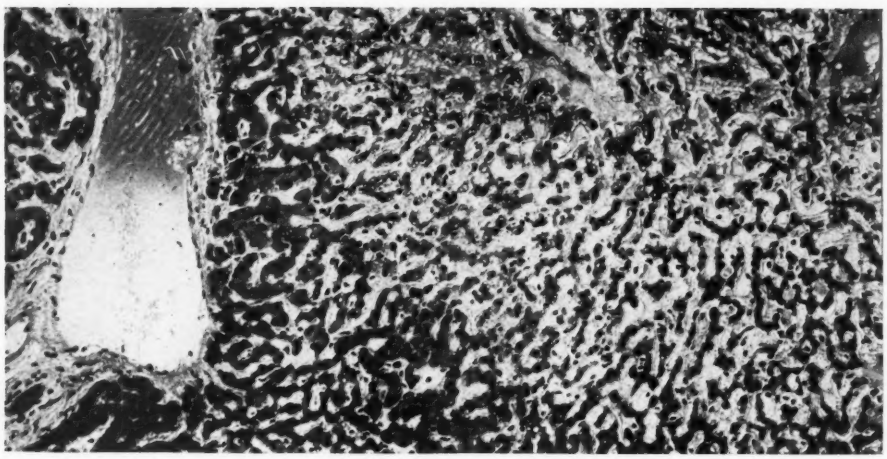

FIG. 4.—Case 5. Twelve hours post mortem. The necrosis has apparently extended. Liver cells are smaller and darker and the perisinusoidal spaces are open. H.E. (×120).

Methylene blue sometimes showed excess of bile pigment in the minute bile channels (" bile thrombi "), especially in the periportal region. Large numbers were seen in ten patients, in general, the most deeply jaundiced. The mean serum bilirubin for this group was 3·7 mg./100 ml. compared with 2·1 mg./100 ml. for the whole series. Iron was not increased either in liver cells or in Küpffer cells. There was no relationship between the increased central brown pigment or bile pigment and hæmosiderosis.

THE COURSE OF CENTRILOBULAR HEPATIC CELL NECROSIS IN HEART FAILURE

If the heart does not respond to therapy the necrosis spreads towards the periphery of the hepatic lobule. This is illustrated by the following case history.

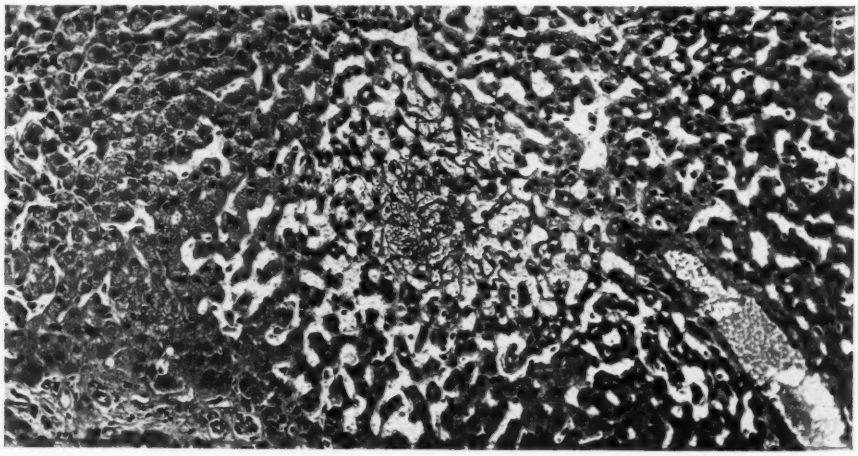

FIG 5.—Case 1. Hypertensive heart failure: 4/4/45. Serum bilirubin, 1·3 mg./100 ml. Grade B lesion. H.E. (×120).

Case 1, H. S., man, aged 55, admitted 1/4/45. Hypertensive heart failure for two months. 4/4/45; serum bilirubin, 1·3 mg./100 ml.; bromsulphalein retention, 36 per cent. Hepatic biopsy showed congestive disorganization of the lobular centres (grade B). In places there was frank hæmorrhage into the central areas. Sinusoids distended and liver cell columns narrowed. No

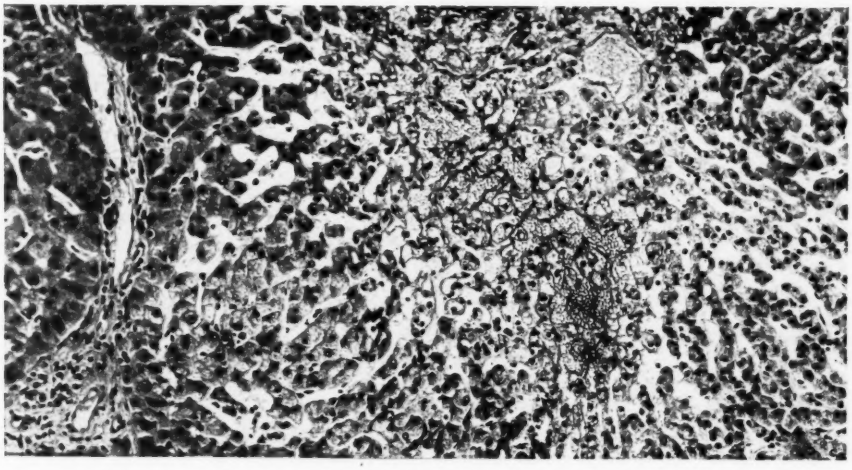

FIG. 6.—Case 1. 17/4/45. Serum bilirubin, 1·0 mg./100 ml. Grade C lesion. H.E. (×130).

fatty change. Portal tracts normal (Fig. 5). Apart from some central condensation of fibres, reticulin pattern normal. 17/4/45—CO, 2·6 l./minute. RAP, 24 cm. saline. Serum bilirubin level, 1·0 mg./100 ml. Second hepatic biopsy—extension of the necrosis (Fig. 6). Inner two-thirds of the lobule completely disorganized. Hæmorrhage persistent. Patient died 23/4/45.

This case record illustrates the rapidity with which liver cell necrosis can increase in the presence of uncontrolled congestive heart failure. Jaundice does not necessarily deepen.

If the cardiac failure responds to treatment the centrilobular necrosis may heal, and even if there is a definite cardiac cirrhosis, hepatic function may be adequate. This is illustrated by the following case history.

Case 2, E. M., man, aged 59, long standing winter bronchitis and pulmonary emphysema. January, 1946, admitted in pulmonary cardiac failure. 8/1/46; serum bilirubin, 1·3 mg.; serum albumin, 2·2 g.; serum globulin, 4·2 g. (all per 100 ml.) 43 per cent retention of bromsulphalein. Urine bilirubin present and urobilinogen excessive. RAP +8 cm. saline, CO, 5·7 l./minute

FIG. 7.—Case 2. Cor pulmonale: 8/1/46. Serum bilirubin, 1·3/100 ml.; 43 per cent retention of bromsulphalein at 30 minutes. Lobular centres show fibrous tissue with some hæmorrhage. Adjoining liver cells show degenerative changes. H.E. (×120).

(high output type); arterial oxygen saturation, 48 per cent. Hepatic biopsy, I. Conspicuous centrilobular congestion with necrosis. Liver cells contain excess golden brown pigment. Centrilobular condensation of reticulin with formation of new connective tissue. Lesion is an early cardiac cirrhosis (Fig. 7). Patient made an unexpectedly good recovery and six months later was no longer in cardiac failure. 13/7/46; serum bilirubin less than 0·5 mg.; serum albumin, 4·1; and serum globulin, 3·3 g., all per 100 ml. Ten per cent retention of bromsulphalein. Urine: no bilirubin or urobilinogen. Hepatic biopsy, II. The acute change has subsided. Necrotic areas replaced by dense collagenous connective tissue in which a few pigmented liver cells remain trapped. Reticulin stains show only black fibres. No new reticulin formation. Early cardiac cirrhosis confirmed (Fig. 8 and 9).

With control of the heart failure there was healing of the liver cell damage. An inactive cardiac cirrhosis remained. This could not have been readily detected by clinical or biochemical means but was demonstrated by hepatic biopsy.

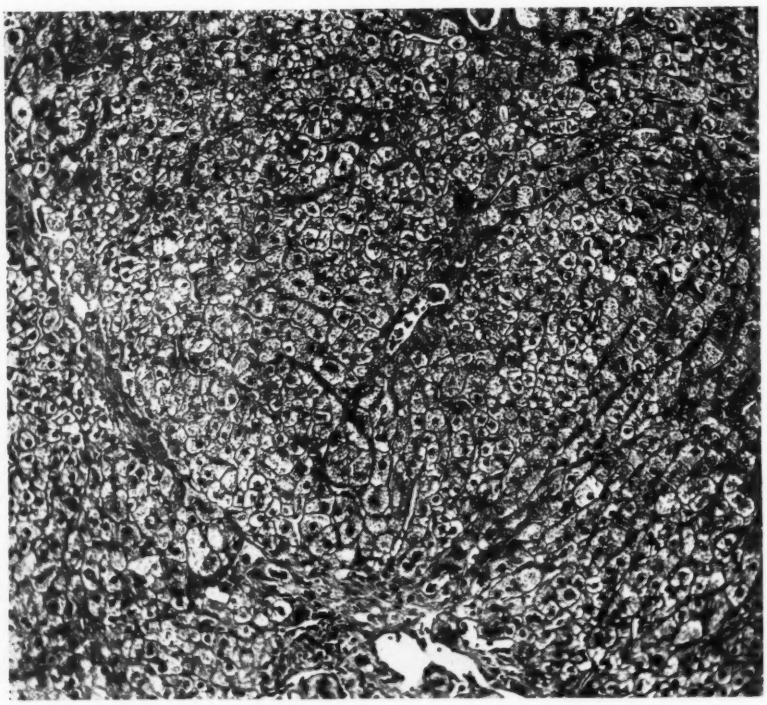

FIG. 8.—Case 2. 13/7/46. Serum bilirubin, 0·5 mg./100 ml.; 10 per cent retention of bromsulphalein at 30 minutes. Inactive cardiac cirrhosis. Liver cells contain their normal complement of glycogen. A portal tract occupies a central position and normal bands of fibrous tissue pass from central area to central area. H.E. (×120).

FIBROUS TISSUE CHANGES AND CARDIAC CIRRHOSIS

In the mildest cases (Grade A) the reticulin pattern is normal. The occasional association of much liver cell damage with an intact reticulin framework is usually seen in acute heart failure of short duration. The next stage is centrilobular reticulin condensation (Fig. 3). Liver cells have been lost from the centres of the lobule and this has resulted in collapse of the reticulin stroma—a very common finding in heart failure.

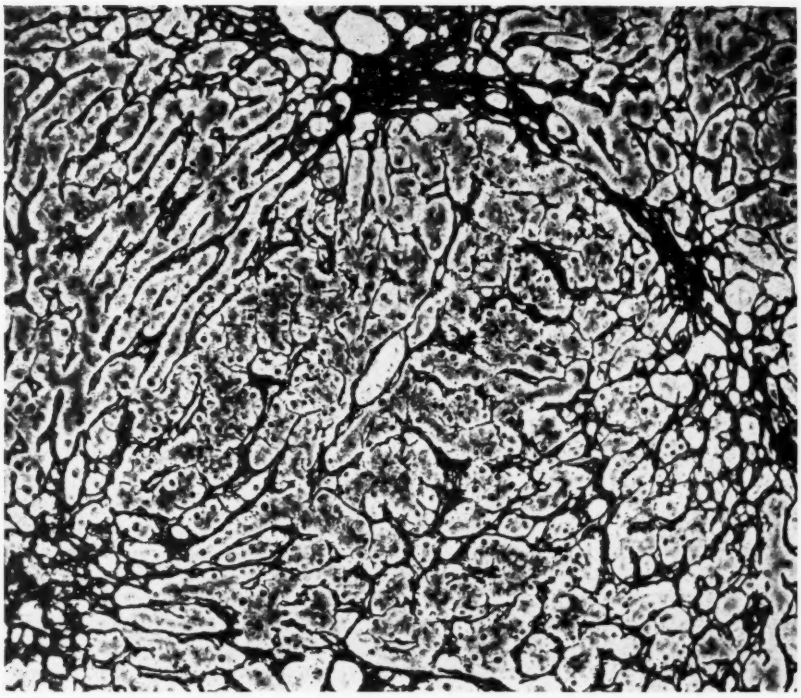

FIG. 9.—Same field as shown in Fig. 11. Reticulin stains confirm the cardiac cirrhosis. (×120).

Then follows centrilobular reticulin proliferation. Not only are the reticulin fibres more closely packed together but there is actual production of new reticulin at the centre of the lubule. This is seen as golden yellow fibres in the silver impregnated sections (Fig. 12). A centrilobular increase in collagen is also found. The central vein is itself thickened and shows a reduplication of reticulin fibres in its wall (phlebosclerosis). The connective tissue extends outwards for a variable distance but does not reach the periphery of the lobule.

If the heart failure continues or relapses, the connective tissue from one central vein joins connective tissue from the central areas of adjoining lobules. The portal areas become surrounded by a ring of fibrous tissue passing from central vein to central vein. This gives the appearance of reversed lobulation. This lesion is a frank cardiac cirrhosis (Fig. 9 and 13). The portal tracts may remain unaffected, but in long standing cases they are often also involved; the bile ducts proliferate, fibroblasts are seen, and sometimes there is also a little round-celled proliferation. When there are changes in both central areas and portal tracts a complex " mixed " picture results (Fig. 15). This may be difficult to distinguish from the usual type of portal cirrhosis. Careful study, however, usually demonstrates that the maximal fibrosis is centrilobular. In some instances nodular regeneration of liver cells may be seen.

Progression of fibrosis in the presence of continuous heart failure is illustrated by the following case history.

Case 3, M. H., woman, aged 26; rheumatic mitral and aortic valvular disease. 21/7/44, admitted in congestive cardiac failure for first time. 26/8/44, patient slightly jaundiced. Serum bilirubin, 2·7 mg./100 ml., 53 per cent retention of bromsulphalein; serum alkaline phosphatase, 8·8 units;

serum albumin, 2·4 g., serum globulin, 2·8 g. (all per 100 ml.). Urine: bilirubin and urobilin present. Hepatic biopsy, I. Intense congestion of the lobular centres, disappearance of liver cells (grade C). Sinusoids dilated with peripheral fatty change (Fig. 10). Condensation of reticulin at the lobular centre; formation of much new connective tissue. Patient progressively more

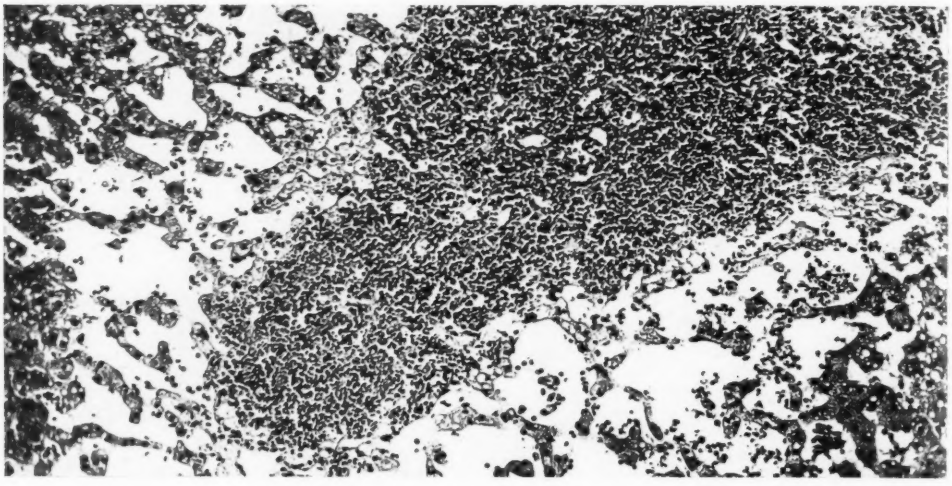

FIG. 10.—Case 3. Mitral and aortic valvular disease: 26/8/44. Serum bilirubin, 2·7 mg./100 ml. Grade C lesion. Extreme centrilobular congestion and necrosis of liver cells with fatty change at the periphery of the lobule. H.E. (×135).

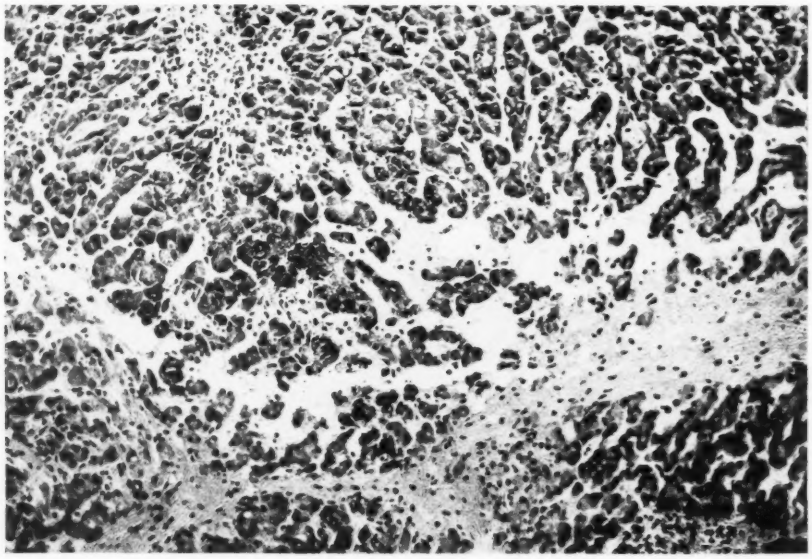

FIG. 11.—Case 3. 16/9/44. Serum bilirubin, 22·0 mg./100 ml. RAP, +29 cm. saline; CO, 2·8 l./minute. Extension of the lesion with linkage of centrilobular areas by bands of fibrous tissue. Surviving liver cells retain their glycogen. Best's carmine. (×120).

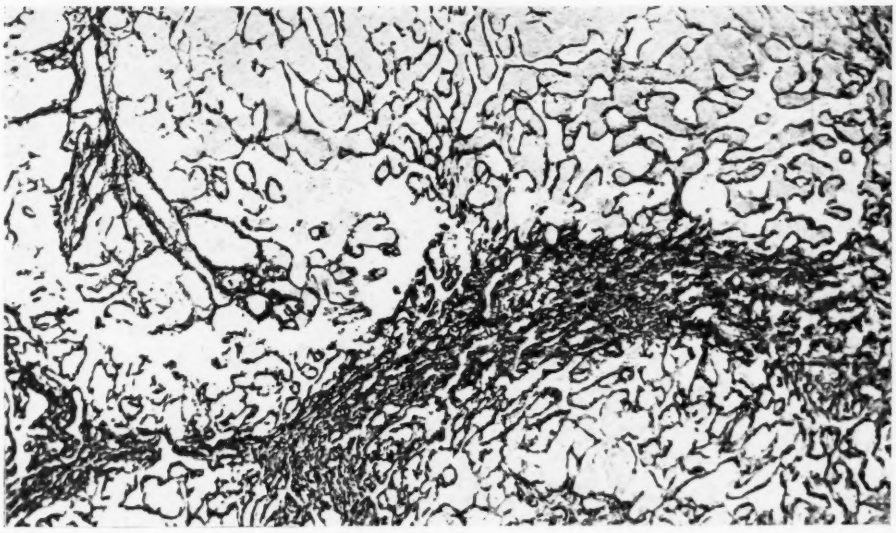

FIG. 12.—Case 3. Reticulin stains show proliferation with bands passing from central area to central area. Modified Foot. (×120).

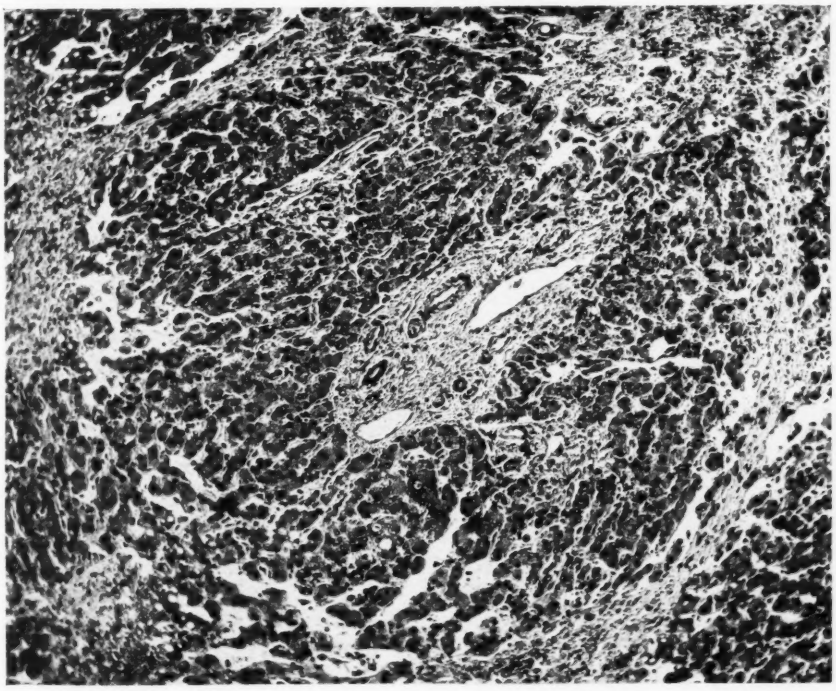

FIG. 13.—Case 3. 26/9/44. Serum bilirubin, 25 mg./100 ml. Post-mortem sections show fibrous tissue bands passing from central vein to central vein. There is " reversed lobulation " and a fully developed cardiac cirrhosis. Portal tracts show only slight fibrosis. H.E. (×90).

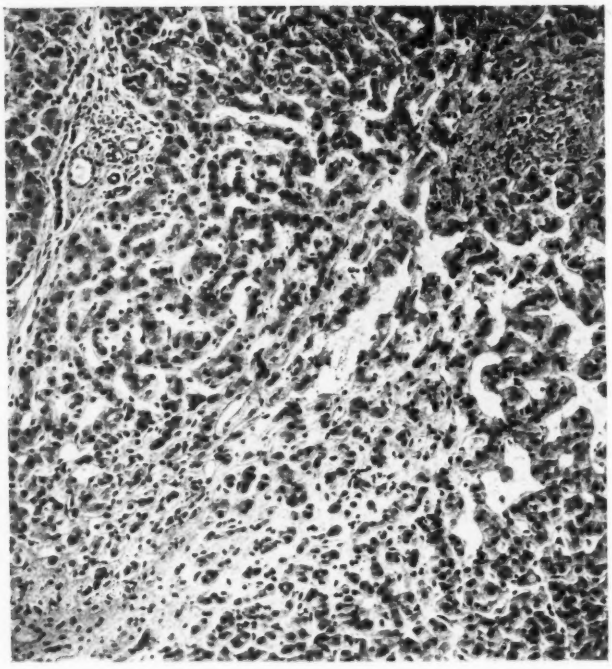

FIG. 14.—Case 4. Mitral stenosis: 15/2/45. Serum bilirubin, 0·5 mg./100 ml.; 10 per cent bromsulphalein at 30 minutes. Fully developed inactive cardiac cirrhosis. Portal tracts are relatively unaffected.

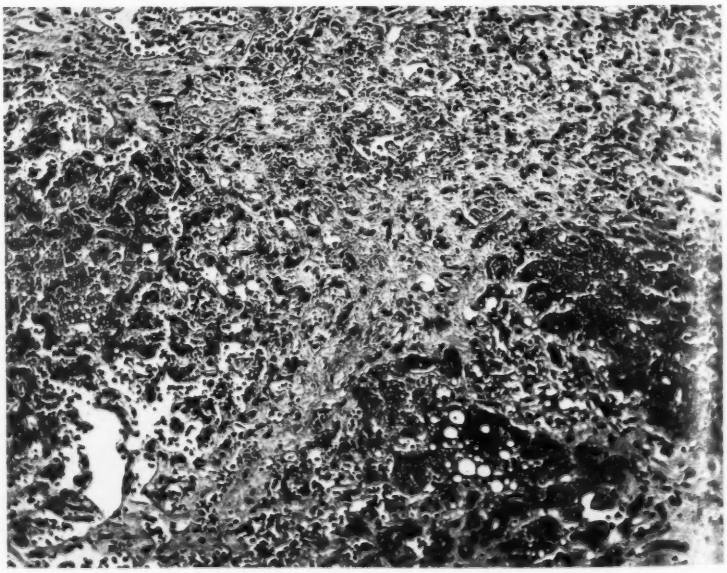

FIG. 15.—Case 4. 25/2/46. Serum bilirubin, 1·6 mg./100 ml.; 31 per cent retention of bromsulphalein at 30 minutes. Post-mortem sections show an active cardiac cirrhosis. Portal tracts are also involved giving a mixed portal and cardiac cirrhosis. H.E. (×120).

deeply jaundiced and on 14/8/44 as yellow as a patient with carcinomatous biliary obstruction. Serum bilirubin, 22·0 mg./100 ml. Cardiac catheterization: RAP +29 cm. saline; CO, 2·8 l./minute. Hepatic biopsy, II (16/9/44). Centrilobular areas linked with adjoining central areas by bands of fibrous tissue. Portal tracts normal (Fig. 11 and 12). Conspicuous bile stagnation, many bile " thrombi " being seen in canaliculi at the periphery of the lobule. 26/9/44, patient died. Final serum bilirubin, 25 mg./100 ml. Post mortem: bile passages patent and full of dark bile; heart: aortic incompetence, mitral stenosis and tricuspid incompetence; no pulmonary or other infarction. Post-mortem hepatic sections: fully developed cardiac cirrhosis. Reversed lobulation, relatively normal portal tracts apparently occupying a centrilobular position. Congestion and disappearance of liver cells adjoining the central vein (Fig. 13). Reticulin stains confirm cardiac cirrhosis.

The regression and healing of the centrilobular necrosis associated with heart failure has already been described (Case 2). If the cardiac lesion is adequately treated, a cardiac cirrhosis may similarly be associated with little functional disturbance. Acute hepatic changes and usually jaundice follow further heart failure, as illustrated by the following case history.

Case 4, E. L., a housewife, aged 38. Many previous hospital admissions with congestive heart failure due to auricular fibrillation and mitral stenosis. Responded well to usual treatment and on 15/2/45 was not in congestive failure. Serum bilirubin less than 0·5 mg.; serum albumin, 4·2 g.; serum globulin, 2·2 g. (all per 100 ml.). Bromsulphalein retention, 10 per cent. Urine, urobilinogen absent. Hepatic biopsy, a fully developed cardiac cirrhosis. Centrilobular bands of mature connective tissue joining bands from adjoining lobules. Portal tracts normal. Some dilatation of central sinusoids but no hæmorrhage. Surviving liver cells normal with normal glycogen and fatty change absent. This lesion is an inactive cardiac cirrhosis (Fig. 14). Patient remained on the verge of heart failure: on 2/2/46 re-admitted in gross congestive failure. 24/2/46: serum bilirubin, 1·6 mg.; albumin, 3·1 g.; globulin, 3·4 g., all per 100 ml.. 31 per cent retention of bromsulphalein. Urine positive for bilirubin and urobilinogen. Patient died 25/2/46. Liver sample by aspiration thirty minutes after death: great increase in connective tissue. Fibrous bands between central areas and also joining portal tracts. A mixed picture of centrilobular " cardiac " cirrhosis and the common " portal " type (Fig. 15).

It is clear that both exacerbations and increasing duration of congestive cardiac failure result in aggravation of the hepatic lesion. Recovery from the failure leads to healing.

The Post-mortem Changes in the Liver in Patients Dying of Heart Failure

In three instances hepatic tissue was obtained less than 24 hours before death and at necropsy. The hepatic changes in the following case are typical.

Case 5, G. S., man, aged 48: cardiac failure due to chronic bronchitis and emphysema. Mildly icteric, serum bilirubin, 3·4 mg./100 ml. Arterial blood 59 per cent saturated with oxygen; CO, 3·5 l./minute and RAP, 16 cm. saline. Hepatic biopsy 2 hours ante mortem. Severe degree of hepatic cell necrosis (grade C: Fig. 2). Twelve hours after death (Fig. 4) the liver cells at the lobular centre had disappeared, leaving shrinkage and nuclear degeneration at the periphery. No normal cells. Cytoplasm darker, due to loss of glycogen. Surviving cells no longer closely packed together but now dissociated. Parasinusoidal spaces opened up; liver cell columns shrunken. Sinusoids contained less blood than in life.

In 14 other instances the ante- and post-mortem differences observed were of the same type as those described above. The increase in the liver changes occurring during the agonal period and immediately post mortem makes autopsy material unreliable for assessing the effects of cardiac failure on the liver in life.

Relation of Hepatic Histology to the Clinical State

(a) *Nature and duration of heart disease.* Hepatic cell necrosis occurred in all forms of heart failure, the severer grades being most frequently found in mitral stenosis. In general, the longer the

patient had been in failure the greater was the extent of underlying damage to the liver. Only 5 of the 18 patients with grade A damage had been in failure for longer than 60 days, whereas 7 of 15 patients in grade B and 12 of the 17 in grade C had been in failure for 60 days or more.

When cardiac cirrhosis existed, mitral stenosis was by far the most frequent accompanying heart lesion. Of the 13 patients with cardiac cirrhosis 11 had mitral stenosis and 2 pulmonary heart disease (Table I). All the patients with mitral stenosis and cardiac cirrhosis had had repeated

TABLE I

HEPATIC RETICULIN CHANGES RELATED TO THE EXTENT OF HEPATIC CELL NECROSIS AND TO THE TYPE OF HEART FAILURE

	Reticulin pattern changes (No. of patients)			
	Normal	Centrilobular condensation	Centrilobular proliferation	Cirrhosis
Extent of hepatic necrosis:				
A	16	1	1	0
B	3	2	3	7
C	4	5	2	6
Type of heart failure:				
Primarily valvular mitral	3	2	2	11
Aortic	4	2	0	0
Cor pulmonale ..	7	1	2	2
Hypertensive	6	1	1	0
Ischæmic	3	2	1	0

episodes of heart failure. The two patients with pulmonary heart disease and cirrhosis were in failure for the first time but the attack in both instances had lasted at least three months.

(*b*) *Circulatory changes.* There was no correlation between right auricular pressure and the extent of hepatic cell necrosis (Fig. 16). Out of 12 patients with the severest grade of hepatic cell necrosis 11 had a cardiac output less than 3·8 l./minute. A significant correlation with low output was not established, however, as many of the patients with minimal lesions had conspicuous lowering of cardiac output (Fig. 16). There was also little relation between liver necrosis and arterial oxygen saturation, but the patients with severe liver necrosis and normal or high cardiac outputs usually had very low arterial oxygen saturations (Fig. 16).

(*c*) *The relation of cardiac cirrhosis to portal hypertension.* The common Laennec cirrhosis often results in portal hypertension. The cirrhotic lesion in heart failure may resemble closely Laennec's cirrhosis and data in 28 patients were scrutinized to decide whether cardiac cirrhosis caused portal venous hypertension.

Superficial abdominal veins were not distended. Hæmatemesis did not occur. In the 28 necropsies œsophageal varicosities were not seen. Mean spleen weight for the 19 patients with cardiac cirrhosis was 175 g. and for the 18 patients without 155 g. The difference is not significant. Spleen histology did not differ. In the 10 patients with cardiac cirrhosis the mean volume of ascitic fluid was 1110 ml., the 18 patients without cardiac cirrhosis had a mean ascitic volume of 1260 ml. It is apparent that cardiac cirrhosis does not add portal hypertension to the clinical or post-mortem picture.

JAUNDICE IN HEART FAILURE

Of the 50 patients, 34 had serum bilirubin levels greater than 1 mg./100 ml. and in 16 the value exceeded 2 mg./100 ml. Moreover, in 8 subjects jaundice was deep with a serum bilirubin greater than 4·5 mg./100 ml. The 3 highest values were 18·0, 21·5 and 22·0 mg./100 ml. and compare with the levels found in mechanical obstruction of the common bile duct.

Jaundice and the extent of liver damage. The serum bilirubin was usually normal in grade A and in only 5 of 18 patients was the level greater than 1 mg./100 ml.; 12 of 15 patients in grade B

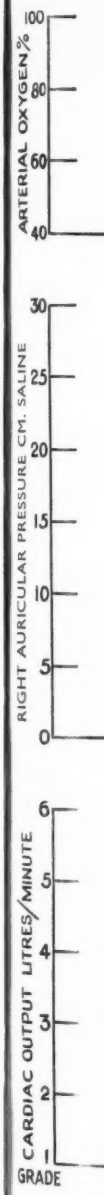

FIG. 16.—T

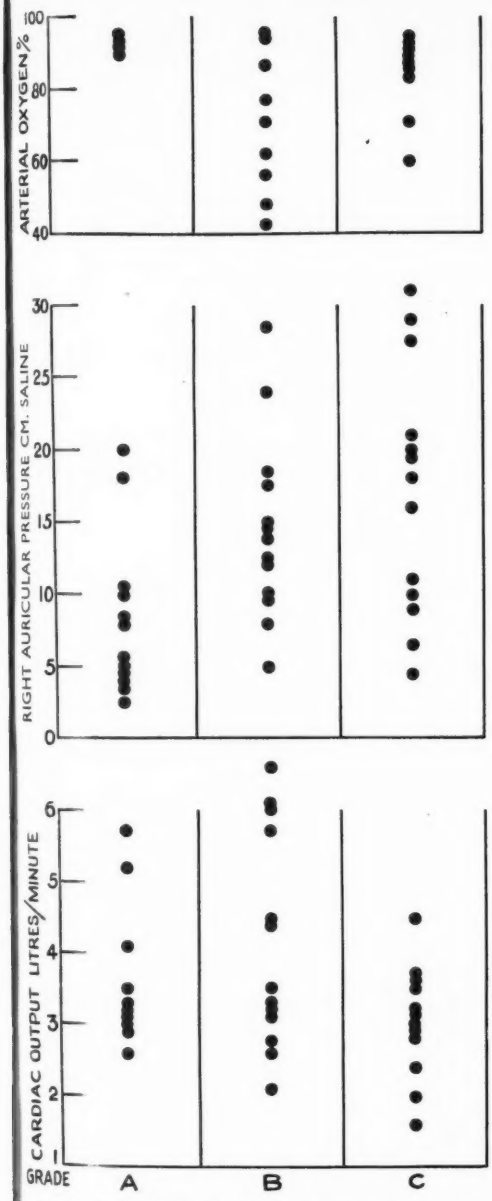

FIG. 16.—The relationship of extent of hepatic necrosis to the cardiovascular changes.

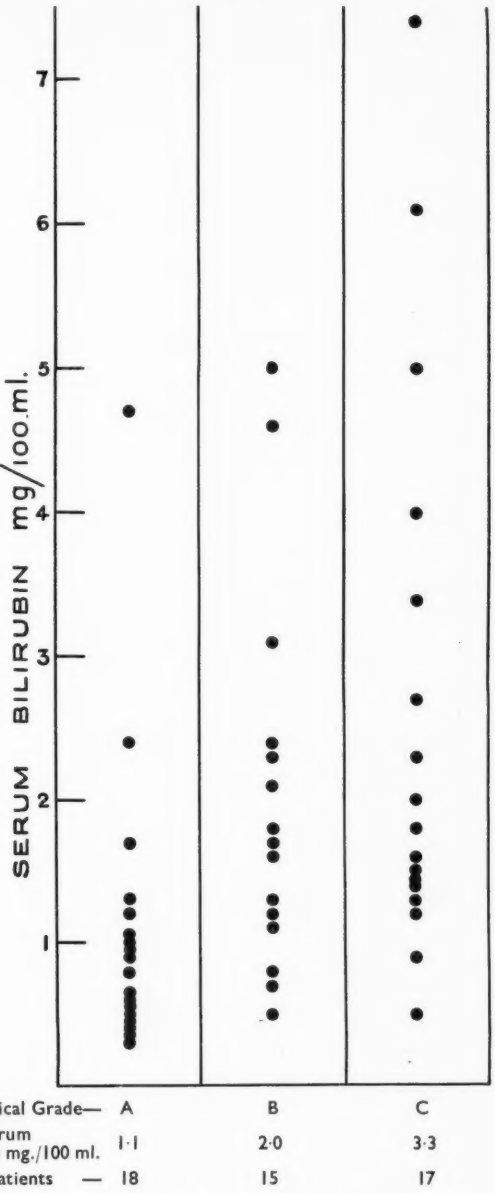

FIG. 17.—The relationship of extent of hepatic necrosis to the serum bilirubin concentration.

and 15 of 17 in grade C had values greater than 1 mg. There was a statistically significant difference between the mean serum bilirubin for grades A and B but none between B and C (Table II). The relation between the necrosis and the depth of jaundice is shown in Fig. 17.

TABLE II

BIOCHEMICAL RESULTS IN 50 PATIENTS WITH HEART FAILURE

Extent of hepatic necrosis	Serum bilirubin mg/100 ml.		Serum alk. phosphatase units/100 ml.		Serum albumin g./100 ml.		Serum globulin g./100 ml.		Bromsulphalein percentage retention at 30 minutes	
	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean
Normal . .	—	(0·5–1)	—	(4–13)	—	(3·4–5·0)	—	(1·5–3·0)	—	(0–10)
Grade A	18	1·1 0·24* (0·5–4·7)†	17	9·3 1·07 (6·0–25·0)	16	4·1 0·10 (3·4–4·7)	16	2·5 0·15 (1·4–3·6)	6	11·3 (2–30)
Grade B	15	2·0 0·33 (0·5–5·0)	15	10·3 1·21 (6·0–20·0)	15	3·5 0·18 (2·2–4·7)	15	2·9 0·17 (1·4–4·2)	7	18·0 (1–48)
Grade C	17	3·3 0·13 (0·9–7·4)	13	12·3 1·03 (4·7–26·0)	12	3·5 0·21 (2·4–5·1)	12	2·9 0·13 (1·6–3·7)	8	24·6 (7–53)
TOTAL	50	2·1 0·19 (0·5–7·4)	45	10·5 0·73 (4·7–26·0)	43	3·7 0·11 (2·2–5·1)	43	2·8 0·12 (1·4–4·2)	21	19·0 2·53 (1–53)

*=standard error of mean.
†=range.

Jaundice and cardiac cirrhosis. As there were no instances of cirrhosis in grade A the comparison has been made between those with and without cirrhosis in grades B and C. The mean serum bilirubin for the 19 patients without cirrhosis was $2{\cdot}0 \pm 0{\cdot}35$ and for the 13 patients with cardiac cirrhosis $2{\cdot}9 \pm 0{\cdot}5$.

Jaundice and the cause of the heart failure. Mild degrees of jaundice may occur with all the common varieties of heart failure—valvular, hypertensive, ischæmic, or pulmonary. Deeper icterus has a closer association with valvular heart disease and in particular with mitral stenosis. Of 16 patients first observed with serum bilirubin greater than 2 mg./100 ml., 12 suffered from mitral stenosis, one from aortic valvular disease, one from ischæmic heart failure, and two from pulmonary heart disease. Eight eventually became deeply jaundiced with a serum bilirubin value greater than 4 mg./100 ml. and of these 7 had mitral stenosis. In 5 there was an associated tricuspid valvular incompetence.

Jaundice and the hæmodynamics of heart failure. There was no correlation between the serum bilirubin values and the cardiac output. A statistical correlation ($r=0{\cdot}78$) was established between the depth of jaundice and the venous filling pressure of the right heart, the patients having very deep jaundice also having very high right auricular pressures. There was no relationship between arterial oxygen saturation and the depth of cardiac jaundice (Fig. 18).

Jaundice and pulmonary infarction. In 42 of the 50 patients there was clear clinical or necropsy evidence of the presence or absence of pulmonary infarction. The distribution is shown in Table II. In all grades of histological severity of liver damage the mean serum bilirubin was higher where there was pulmonary infarction than where this was absent. Infarction was noted in all the varieties of heart failure except ischæmic, but was most frequently associated with mitral stenosis. These

patients with mitral stenosis in whom the serum bilirubin was greater than 2 mg./100 ml. and in whom there was no pulmonary infarction usually had an accompanying incompetence of the tricuspid valve.

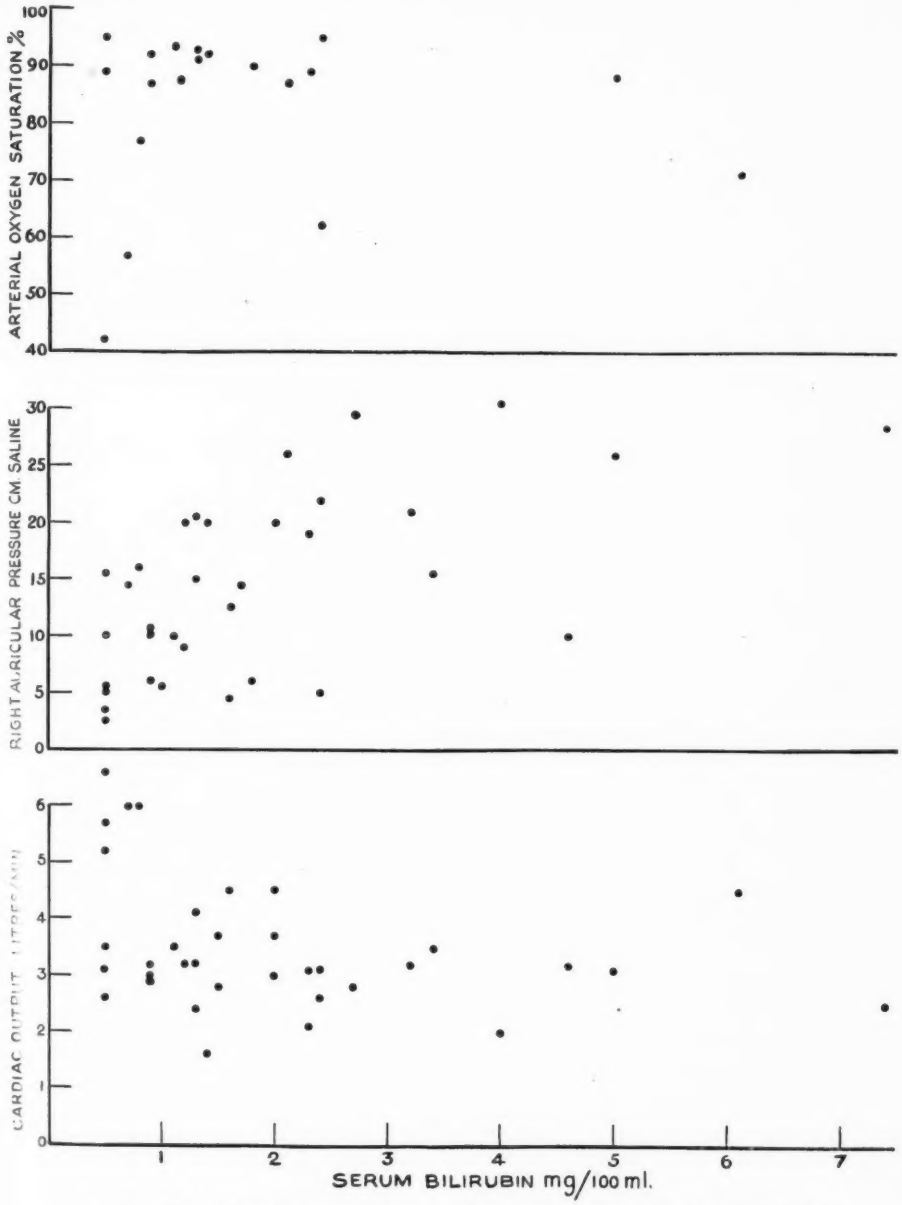

FIG. 18.—The relationship of cardiovascular changes to the serum bilirubin concentration.

In two instances the hepatic lesion and circulatory changes were minimal although there was visible icterus. Both patients had clear evidence of pulmonary infarction and it seems possible that this was related to the jaundice. The following case history is illustrative.

Case 6, T. E., cobbler, aged 35, with mitral stenosis. 2/1/46, sudden cough and increasing dyspnœa. Slightly jaundiced, auricular fibrillation, mild congestive heart failure. Serum bilirubin, 2·4 mg./100 ml.; serum alkaline phosphatase, albumin, globulin and colloidal gold test

TABLE III

THE RELATION OF SERUM BILIRUBIN CONCENTRATION AND PULMONARY INFARCTION

No. of patients	Mean serum bilirubin	Histology of liver Grade						Type of heart failure (No. of cases)				
		A		B		C						
		No.	Serum bilirubin (mean)	No.	Serum bilirubin (mean)	No.	Serum bilirubin (mean)	Mitral valvular	Aortic valvular	Cor pulmonale	Hypertensive	Ischæmic
Without pulmonary infarction												
28	1·4	11	0·9	10	1·6	7	2·1	7	2	11	4	4
With pulmonary infarction												
14	3·2	3	2·6	4	3·1	7	3·5	9	2	1	2	0

normal. Bromsulphalein test, 14 per cent retention. Urine: excess urobilinogen (15·6 mg. in 24 hours); bilirubin. 3/1/46, cough with brown-stained sputum. Hepatic biopsy: slight centrilobular distension of sinusoids but liver histologically normal. CO, 3·1 l./minute and the RAP, +5 cm. saline. Arterial oxygen saturation 95 per cent. Patient made an uninterrupted recovery. 7/1/46, serum bilirubin level less than 0·5 mg./100 ml.

Bromsulphalein. The power of the liver to excrete bromsulphalein diminished with increasing severity of liver cell necrosis (Table II). The relationship of serum bilirubin to the results of the bromsulphalein test were not nearly so close (e.g. Case 6) and in three instances the serum bilirubin level was greater than 3 mg./100 ml. although there was less than 15 per cent retention of bromsulphalein in the 30-minute specimen.

Urinary urobilin, urobilinogen, and bilirubin. In all but 4 (3 with a grade A lesion, 1 with grade C) urinary urobilinogen was present in excess. In 10 patients the 24-hourly excretion of urobilinogen was quantitatively estimated; in all but 1 there was an increase (Table IV). Although the iodine test commonly used to detect bilirubin was positive in only 10 subjects the more sensitive methylene

TABLE IV

URINARY UROBILINOGEN AND BILIRUBIN IN HEART FAILURE

Grade	Positive qualitative tests				Quantitative urobilinogen * mg./24 hours		
	No. of patients	Urobilinogen	Bilirubin		No. of patients	Mean	Range
			Iodine	Methylene blue and diazo			
Normal	—	0	0	0	—	—	0–4
A	18	15	1	3	2	8·9	2·2–16
B	15	15	3	10	4	12·5	4·5–40
C	17	16	6	11	4	14·2	4·3–45

* Normal excretion is 0–4 mg./24 hours.

blue and diazo tests were positive in 24 patients. Positive results were most frequent in the patients with the more severe liver damage and with the higher serum bilirubin values.

Other Biochemical Data

Serum alkaline phosphatase was usually normal (Table II). In 5 of 50 subjects the value was greater than the 13 units taken as the upper limit of normal. However, the concentration was always less than the 30 units used to differentiate primary parenchymatous from obstructive jaundice (Sherlock, 1946). Some of the patients with the deepest jaundice had the lowest values for alkaline phosphatase; nor was the serum phosphatase level related to cirrhosis.

Although the mean values for total serum protein, for serum albumin and for serum globulin were within normal limits (Table II) there was a great deal of variation in the individual patient. Twelve of 43 patients had a serum albumin value less than the normal lower limit of 3·4 g./100 ml. and 18 patients had serum globulin levels above the upper normal limit of 3 g./100 ml. The serum proteins were occasionally greatly disturbed; in 4 patients serum albumin was less than 2·5 g./100 ml. and in 4 other patients also the serum globulin level was greater than 3·5 g./100 ml.

Low serum albumin values occurred only in grades B and C. There was a significant difference between the values of grade A compared with the severer grades B and C. Although 4 of the 16 patients in grade A had conspicuous globulin increases the changes were common in grades B and C, 8 of the 15 patients in grade B and 6 of the 12 in grade C showing an increase. There was no significant difference between the serum protein values of those with and those without cardiac cirrhosis. Little relation was found between the duration of the congestive failure and the serum protein values.

Diminution of serum albumin was most frequently encountered in patients suffering from mitral stenosis or *cor pulmonale*. Six of 17 patients with mitral stenosis and 5 of 9 patients with pulmonary heart failure had changing values lower than 3·4 g./100 ml. Serum protein, and particularly albumin, passes to a certain extent into œdema fluid. The patients with the worst œdema would be expected to have the lowest serum albumin and highest serum globulin values. This proved to be the case and might partially explain the association of depressed serum albumin and raised serum globulin with mitral stenosis and *cor pulmonale* in which œdema tends to be greatest.

A positive colloidal gold test was obtained in only 4 of 36 patients, 2 of the positive results occurring in grade B and 2 in grade C. Two of the patients had cardiac cirrhosis; the remaining 11 patients with cardiac cirrhosis showed a negative colloidal gold test.

Discussion

Post-mortem Changes in the Liver in Heart Failure

The rapid autolytic changes in the diseased liver after death have been referred to above, and the present observations confirm those of Popper (1948), and show that post-mortem hepatic autolysis is particularly rapid in heart failure. There is a discrepancy between the incidence of fatty change in our series and that usually described in textbook accounts of heart failure based on selected necropsy material, which taken from the liver in heart failure is almost useless for correlation with *in vivo* changes.

Centrilobular Hepatic Necrosis in Heart Failure

The liver is particularly sensitive to oxygen lack and the integrity of the liver cell depends on an adequate oxygen supply. The liver cells at the centre of the lobule receive blood at a lower oxygen tension than at the periphery (Blalock and Mason, 1936) and are therefore more susceptible to any fall in the oxygen supply to the liver. Anoxia is known to cause both degeneration of central liver cells (Martin, Bunting, and Loevenhart, 1916), and dilatation of sinusoids (Seneviratne, 1949).

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In man, as the cardiac output diminishes, the hepatic blood flow diminishes in proportion (Myers and Hickam, 1948). The oxygen supply to the liver decreases with diminishing cardiac output. Centrilobular hepatic necrosis in heart failure ought therefore to bear some relation to the degree of depression in cardiac output, but there is a group with high cardiac output showing conspicuous centrilobular necrosis in whom other factors such as low arterial oxygen saturation and anæmia may be involved.

The oxygen supply to the liver depends not only on the hepatic blood flow but also on the oxygen content of the portal venous and hepatic arterial blood. A correlation between arterial oxygen unsaturation and the extent of centrilobular necrosis might be anticipated. Very few estimations were available but a positive correlation was not established. However, six patients with pulmonary heart disease with high cardiac output did have low arterial oxygen saturations. Five of these had grade B liver cell necrosis and in these subjects the reduced arterial oxygen saturation seemed an important factor in the production of the liver lesion.

Increased pressure in the hepatic veins might conduce to the centrilobular necrosis. Although patients with the maximal hepatic necrosis often have high right auricular and presumably hepatic venous pressures, the correlation was not constant. The patient with constrictive pericarditis who probably had the highest hepatic venous pressure also showed very severe centrilobular necrosis, a condition found in most patients with constrictive pericarditis. As Bolton (1914) pointed out it is doubtful whether the centrilobular changes produced by " passive " venous congestion are mechanical since the rise of pressure must extend right through the lobule to the portal veins. He believed them to be due to " a nutritional disturbance and presumably oxygen lack resulting from blood flow changes." Another factor determining the extent of the necrosis is the duration of the heart failure, as shown in the present series.

Cardiac Cirrhosis

Heart failure can undoubtedly produce a centrilobular cirrhosis. The relative rarity of this condition is probably related to the infrequency of prolonged heart failure. Most patients die in the stage of centrilobular reticulin condensation and never pass to the proliferative regenerative phase. Repeated episodes of failure are necessary for the development of full cardiac cirrhosis. Patients with rheumatic mitral stenosis, responding intermittently to treatment, are therefore particularly prone to develop cardiac cirrhosis. If patients with other forms of heart failure survive for a sufficient length of time they too can develop the same lesion. This is illustrated by the two patients with chronic *cor pulmonale* who survived three months and showed cardiac cirrhosis.

Although the connective tissue in heart failure is primarily centrilobular, in the later stages the portal tracts become involved. Fibrous bands link not only central areas but also portal tracts (Fig. 15). This may account for the reported frequency of portal cirrhosis in heart failure (Katzin, Waller and Blumgart, 1939). Serial hepatic biopsies show that the essential cirrhosis of heart failure is a centrilobular one and involvement of the portal tracts is merely a later confusing feature.

The patients with cardiac cirrhosis were not more deeply jaundiced than those without; neither was there any difference in the serum protein values or the colloidal gold test. Cardiac cirrhosis did not seem to be causing intrahepatic vascular obstruction. Moreover, if the heart failure is controlled the acute hepatic changes disappear and the liver shows only avascular fibrous bands passing between central veins. Blood biochemistry returns to normal, as in Case 2. The hepatic lesion is quiescent or latent. This is analogous to the latent cirrhosis sometimes resulting from acute " viral " hepatitis (Sherlock, 1948). It is uncertain whether latent cardiac cirrhosis can eventually lead to portal venous hypertension. This consideration is important in constrictive pericarditis with associated centrilobular cirrhosis. Surgery may relieve the cardiac embarrassment and the cirrhosis will become latent. Other things being equal, cardiac cirrhosis should not contraindicate operation on patients with constrictive pericarditis.

Jaundice in Heart Failure

Although frank jaundice is rare, the serum bilirubin in heart failure is usually increased (Jolliffe, 1930; Kugel and Lichtman, 1933; Routier *et al.*, 1935; Chávez *et al.*, 1943). The present findings also demonstrate this. There are various causes of cardiac jaundice.

(A) Hepatogenous jaundice. This implies that in heart failure the liver cells are inadequate to excrete the bile pigment. The impaired bromsulphalein test is in keeping with this, and, in general, the greater the extent of liver cell necrosis the deeper the icterus (Fig. 17). There are many exceptions, and histological liver cell damage cannot entirely explain cardiac jaundice.

(B) Obstructive jaundice. Eppinger (1937) believed that cardiac jaundice was due to obstruction of bile capillaries both by pressure on the outside by distended veins and by inspissated bile thrombi within. The obstruction theory may be related to the height of the venous pressure within the hepatic lobule. The normal biliary secretory pressure is 20–30 cm. water (McMaster, Broun and Rous, 1923). Many patients with heart failure have right auricular pressures of 20 cm. saline. The hepatic vein pressure may be assumed to be higher than this and may be greater than the pressure at which bile can be secreted. A mechanical obstruction to the intralobular bile canaliculi might thus exist. Moreover, patients with deep jaundice often have very high right auricular pressures (Case 3). The close association of tricuspid valvular incompetence (with presumably high hepatic venous pressures) and deep jaundice has already been noted.

Coagulation of bile in the minute canaliculi to form " bile thrombi " is commonly regarded as evidence of biliary obstruction. Bile thrombi are conspicuous in the livers of patients with deep cardiac jaundice, and are seen whenever jaundice is deep and particularly when the bile is viscid, as in hæmolytic crises. In addition, the centrilobular destruction of liver cells and hæmorrhage in heart failure may themselves disorganize the bile canaliculi and produce stagnation of bile and hence thrombi.

Other evidence against the hepatic venous pressure-obstructive theory of cardiac jaundice may be given. The relationship between high venous pressure and jaundice is not constant (Fig. 18) and some patients with very high right auricular pressures are not jaundiced. At necropsy the gall bladder and bile passages, even with the deepest jaundice, are full of dark bile. The fæces are perhaps darker than normal and do not suggest biliary obstruction. Further, the biochemical data are unlike those of biliary obstruction. Serum alkaline phosphatase is normal as are the blood cholates (Sherlock and Walshe, 1946). Urobilinogen is present in excess in the urine. Intrahepatic biliary obstruction related to high venous pressure is therefore unlikely to be an important cause of cardiac jaundice.

(C) Hæmolytic jaundice. The icterus of heart failure is often related to hæmorrhages into the tissues, particularly pulmonary infarction. The hæmoglobin in the tissues becomes changed to bilirubin. The excess of pigment cannot be excreted by a liver damaged by heart failure, and jaundice results (Kugel and Lichtman, 1933).

There are many points in favour of this hypothesis. There is an excess of iron pigment in some tissues in heart failure. Even without frank infarction the pulmonary alveoli usually contain " heart failure " cells. These macrophages show iron pigment presumably derived from red blood corpuscles. Bilirubin must also have been formed constituting an additional excretory load on the liver. In one patient with pulmonary infarction the serum bilirubin was on the whole higher than those without, but there were many exceptions. In some patients jaundice developed after infarction although the right auricular pressure and cardiac output were not greatly changed and liver biopsy showed only minimal histological changes (Case 6). In these patients jaundice could only be associated with infarction. All the patients with minimal liver cell damage who were jaundiced had clear evidence of pulmonary infarction. The occasional observation of increased serum bilirubin values with relatively normal results for the bromsulphalein retention tests also suggested a hæmolytic jaundice. The very dark bile contained in the full bladder and bile ducts, the excess of urobilin in the urine, and the other biochemical findings in the blood were compatible with hæmolytic icterus.

At the same time pigment overload cannot be the only cause of cardiac jaundice. Rich and Resnik (1926) introduced into the tissues of patients with heart failure a volume of blood equal to that found in pulmonary infarctions and failed to increase the serum bilirubin. Although bilirubinuria is not found in hæmolytic icterus, it was frequent in our patients with cardiac jaundice. Finally, jaundice occurred without pulmonary infarction. It was especially conspicuous in association with tricuspid incompetence in which pulmonary vascular congestion is minimal (Case 3).

Diagnosis of Cardiac Cirrhosis

That clinical recognition of cardiac cirrhosis is usually impossible is suggested by the present finding, and by the work of Boland and Willius (1938). It should be suspected in mitral disease with repeated episodes of heart failure especially if there is an associated tricuspid valvular incompetence. Most patients with heart failure and deep jaundice also have a cardiac cirrhosis, but most patients in whom cirrhosis is present will give no clinical indications of this lesion.

Summary

Sections of liver were obtained by aspiration biopsy or occasionally by necropsy from 50 patients in congestive heart failure and from one patient with constrictive pericarditis. A full post-mortem examination was carried out in 28 subjects. Changes occurring in the agonal and immediate post-mortem periods were such that necropsy sections proved unreliable for assessing the effects of cardiac failure on the liver.

Centrilobular hepatic necrosis was almost invariable. If the heart failure worsened the necrosis spread peripherally whereas if the cardiac condition responded to treatment the liver lesion healed.

Connective tissue changes originated at the centre of the liver lobules. Reticulin condensation occurred first; this was followed by reticulin proliferation and eventually spread of connective tissue from central vein to adjoining central veins giving a cardiac cirrhosis. Cardiac cirrhosis became latent if the heart disease was amenable to treatment.

Structural changes in the liver were perhaps related to circulatory changes, namely, reduction in cardiac output, diminution of the arterial oxygen saturation, height of the hepatic venous pressure, and also to the duration of heart failure.

A raised serum bilirubin was very common; frank jaundice was rare and usually confined to patients with mitral stenosis and tricuspid valvular incompetence. The mean serum bilirubin value was higher in the patients with the severer grades of hepatic cell necrosis and when there was evidence of associated pulmonary infarction. There was no constant association between serum bilirubin values and cardiac output or arterial oxygen unsaturation. However, patients with deep jaundice tended to have very high right auricular pressures.

The power to excrete bromsulphalein diminished with increasing severity of liver cell necrosis. Urine urobilinogen was increased. Bilirubin was often detected in the urine. Serum alkaline phosphatase and total and differential protein values were usually normal. The serum colloidal gold test was usually negative.

It was concluded that cardiac cirrhosis has no specific clinical, blood biochemical, or circulatory associations, and that it does not cause intrahepatic portal venous obstruction.

The complexity of cardiac jaundice has been discussed. Support can be found for hepatocellular, obstructive, and hæmolytic theories. In most patients multiple factors are present and the exact cause of the jaundice cannot be determined.

The histological preparations were made by Mr. J. C. Griffin and the technical staff of the Pathology Department of the Postgraduate Medical School of London. Mr. E. V. Willmott took the microphotographs. I should li

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REFERENCES

Bernstein, M., LeWinn, E. B., and Simkins, S. (1942). *J. Lab. and clin. Med.*, **28**, 1.
Blalock, A., and Mason, H. F. (1936). *Amer. J. Physiol.*, **117**, 328.
Boland, E. W., and Willius, F. A. (1938). *Arch. intern. Med.*, **62**, 723.
Bolton, C. (1914). *J. Path. Bact.*, **19**, 258.
Chávez, I., Sepúlveda, B., and Ortega, A. (1943). *Amer. J. med. Ass.*, **121**, 1276.
Eppinger, H. (1937). *Die Leberkrankheiten*, J. Springer, Vienna.
Gellis, S. S., and Stokes, J., Jr. (1945). *J. Amer. med. Ass.*, **128**, 782.
Haslewood, G. A. D., and King, E. J. (1937). *Biochem. J.*, **31**, 920.
Helm, J. D., and Machella, T. E. (1942). *Amer. J. digest. Dis.*, **9**, 141.
Iversen, P., and Roholm, K. (1939). *Acta med. scand.*, **102**, 1.
Jolliffe, N. (1930). *J. clin. Invest.*, **8**, 419.
Katzin, H. M., Waller, J. V., and Blumgart, H. L. (1939). *Arch. intern. Med.*, **64**, 457.
Kiernan, F. (1833). *The Anatomy and Physiology of the Liver*, J. H. Green, Philosophical Transactions, Royal Soc. of London.
King, E. J., and Armstrong, A. R. (1934). *Canad. med. Ass. J.*, **31**, 376.
——, Haslewood, G. A. D., and Delory, G. E. (1937). *Lancet*, **1**, 886.
——, ——, ——, and Beall, D. (1942). *Ibid.*, **1**, 207.
Kugel, M. A., and Lichtman, S. S. (1933). *Arch. intern. Med.*, **52**, 16.
Maclagan, N. F. (1944). *Brit. J. exp. Path.*, **25**, 15.
McMaster, P. D., Broun, G. O., and Rous, P. (1923). *J. exp. Med.*, **37**, 685.
McMichael, J., and Sharpey-Schafer, E. P. (1944). *Brit. Heart J.*, **6**, 33.
Martin, G. H., Bunting, C. H., and Loevenhart, A. S. (1916). *J. Pharmacol.*, **8**, 112.
Myers, J. D., and Hickam, J. B. (1948). *J. clin. Invest.*, **27**, 620.
Pollock, M. R. (1945). *Lancet*, **2**, 626.
Popper, H. (1948). *Arch. Path.*, **46**, 132.
Rich, A. R., and Resnik, W. H. (1926). *Bull. Johns Hopk. Hosp.*, **47**, 75.
Routier, D., Cottet, J., and Molinghen, P. (1935). *Arch. Mal. Appar. dig.*, **25**, 801.
Seneviratne, R. D. (1949). *Quart. J. exp. Physiol.*, **35**, 77.
Sherlock, S. (1945). *Lancet*, **2**, 397.
—— (1946). *J. Path. Bact.*, **58**, 523.
—— (1948). *Lancet*, **1**, 817.
——, and Walshe, V. (1946). Unpublished observations.
Watson, C. J. (1937). *Arch. intern. med.*, **59**, 196.

THE EFFECT OF PRISCOL ON THE PERIPHERAL VENOUS PRESSURE

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It seems established that the increase of venous pressure in congestive heart failure cannot be explained on a purely mechanical basis. Neither the back pressure theory which explains the rise of venous pressure as being due to damming of blood behind the failing heart, nor the hypothesis that the rise in venous pressure is caused by an increase of blood volume due to retention of salt and water has proved entirely satisfactory. Other regulating mechanisms have, therefore, recently come into the foreground.

McMichael (1949), in an elucidating review of cardiac venous congestion, emphasizes the role of venomotor regulations in congestive heart failure for maintaining and raising the venous pressure. Two pathways have been shown to be active: (i) the autonomic nervous system and (ii) changes in the composition of blood gases. Lewis and Landis (1930) observed dilatation of the veins of the arm and hand following sympathectomy, and this relaxation was shown to be independent of local temperature. Papper and Imler (1944) observed dilatation of the leg veins after sympathectomy and thought that diminution of the venous tone was the cause of this change. Gollwitzer-Meier and Bohn (1930) have shown that increase in the carbon dioxide content of the blood brought about contraction of veins through the medium of the venomotor nerves, which are included in the sympathetic fibres; they believe that this venoconstriction is caused by changes in the acidity of the blood flowing through the vasomotor centres. Starr (1943) reported that in asphyxia there is an increase in the arterial and venous pressure which is apparently caused by anoxia. Little (1949) recently suggested, from an analysis of existing published data, that a decrease in mixed venous CO_2 is the common factor in heart failure that stimulates increased cardiac output and, through venoconstriction, decreased venous capacity. From these observations it is apparent that the tone of the muscular wall of the veins is influenced by venomotor regulation (Henderson, 1943).

The introduction of sympathicolytic drugs makes it possible to study in a more detailed manner the possible role of the autonomic nervous sytem in the production of an increased venomotor tone in heart failure. Relman and Epstein (1948) observed the effect of tetraethylammonium chloride (TEAC) on venous and arterial pressures in congestive heart failure of varying ætiology. This drug blocks transiently the synapses between the preganglionic and postganglionic fibres of the sympathetic nervous system. They found that TEAC caused a significant fall in venous pressure and some decrease in arterial pressure. After administration of digitalis two cases of heart failure lost their initial responsiveness to TEAC. Hayward (1948) reported observations in six patients suffering from hypertensive heart failure. He found that administration of tetræthylammonium bromide led to a fall in the blood pressure and a decrease of the venous pressure. These patients also experienced a temporary relief of orthopnœa and dyspnœa.

Hereunder we are reporting the effect of another sympathicolytic drug on the peripheral venous pressure. Priscol (2-benzyl-imidazoline-hydrochloride) blocks the sympathetic motor pathways

by action on the nerve terminals in smooth muscle (Nickerson and Goodman, 1946), but also counteracts the constrictive effects of epinephrine-like substances, which are formed at the vascular myoneural junction (Meyer, 1941). It is therefore considered to be an adrenolytic and sympathicolytic drug. Clinical observations have shown that it is a potent peripheral vasodilatator (Grimson *et al.*, 1948).

Material and Methods

Venous pressure was measured directly in an anticubital vein with a No. 18 or No. 19 gauge needle connected to an upright manometer and to a container holding saline solution. The measurements were taken after the patient had been resting in a recumbent position for half an hour. The zero point was placed at 4·5–5 cm. below the level of the sternocostal junction of the fourth rib. In instances where repeated measurements were taken the same vein was used. Arterial blood pressure was measured by sphygmomanometer and the heart rate was counted. After repeated estimation of venous pressure, pulse rate, and blood pressure had established a constant base line, 10 mg. priscol was injected intravenously through a fresh venipuncture on the opposite arm. All the measurements were repeated regularly during 30–40 minutes thereafter, the maximum effect of the drug appearing after 3–8 minutes; and after 20 minutes there was a return of the measurements to the values preceding injection. Twenty-two subjects were studied in this manner. Group I consisted of five control subjects with normal arterial and venous pressure. Group II contained four cases of essential hypertension without heart failure. Group III included three cases of hypertensive and arteriosclerotic heart disease with congestive heart failure. Group IV consisted of six cases of valvular heart disease with congestive heart failure. Group V contained four cases of chronic cor pulmonale with marked cyanosis and congestion. One patient of the fourth group and two of the fifth group were studied before and after full digitalization.

Results

The results are summarized in Tables I, II, III, IV, and V which correspond to the numbers of the groups mentioned above. In the controls (Table I) the venous pressure rose in three patients

TABLE I

Controls Treated with Priscol

Diagnosis (Group I)	Age	Sex	Heart rate per minute		Blood pressure mm. Hg.		Mean arterial pressure mm./Hg.		Venous pressure mm./norm. saline	
			Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change
Jejunospasm (B.I.)	55	M	72	+4	120/75	+15/0	90	+5	70	+5
Diabetes mellitus (L.J.) ..	30	M	80	−4	130/90	+10/0	103	+4	97	+28
Gastric ulcer (A.H.)	55	M	80	+8	110/80	+5/0	90	+2	30	+30
Duodenal ulcer (M.A.) ..	24	M	76	+4	110/80	0/−10	90	−7	70	−10
Jejunal ulcer (Z.J.)	48	M	64	−4	115/75	0/0	88	0	45	−5

TABLE II

EFFECTS OF PRISCOL ON HYPERTENSION WITHOUT HEART FAILURE

Diagnosis (Group II)	Age	Sex	Circulation time (secs.)	Heart rate per minute		Blood pressure mm./Hg.		Mean arterial pressure mm./Hg.		Venous pressure mm./norm. saline	
				Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change
Essential hypertension (K.J.)	43	M	15	68	+8	170/115	+20/+5	133	+10	50	+10
Essential hypertension (H.N.)	65	M		80	+16	170/110	−20/−20	130	−20	90	−5
Essential hypertension (S.S.)	59	F	11	86	−8	140/80	−20/−10	100	−13	85	+15
Essential hypertension (R.Ch.)	64	F	14	80	+4	170/95	−5/0	120	−2	65	+15

and in the other two there was a slight fall. The blood pressure increased somewhat in the three patients who showed a rise in the venous pressure, and in the other two it either decreased or did not change at all. In the patients with hypertension but without heart failure (Table II) there was an increase of the venous pressure in three and a slight drop in the fourth. The blood pressure increased in one of them and decreased in the remaining three. In Group III (hypertensive and arteriosclerotic heart disease with congestive heart failure) the venous pressure invariably dropped, the decrease ranging from 12 to 80 mm. saline. The blood pressure increased slightly in one and decreased or did not change at all in the other two. Six patients with valvular heart disease and congestive heart failure (Table IV) showed a uniform response to the administration of priscol. The venous pressure dropped in all instances, the range being from 5 to 28 mm. saline. The blood pressure, too, fell in every one of them (from 5 to 20 mm. Hg.). Patients with chronic cor pulmonale and marked congestion (Table V) showed the most pronounced fall of the venous pressure; the drop ranged from 25 to 146 mm. saline; the blood pressure fell in three of this group (5–15 mm. Hg), while in the fourth there was no change.

TABLE III

EFFECTS OF PRISCOL IN HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE WITH HEART FAILURE

Diagnosis (Group III)	Age	Sex	Circulation time (secs.)	Heart rate per minute		Blood pressure mm./Hg.		Mean arterial pressure mm./Hg.		Venous pressure mm./norm. saline	
				Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change
Arteriosclerotic heart disease (L.J.)	66	M	28	88	+12	130/85	+10/+5	100	+7	180	−80
Hypertensive heart disease (D.W.)	51	F	25	68	+4	220/130	0/0	160	0	132	−12
Hypertensive heart disease (S.A.)	55	F	15	76	+4	170/95	−5/0	120	−2	100	−11

TABLE IV

EFFECTS OF PRISCOL IN VALVULAR HEART DISEASE WITH HEART FAILURE

Diagnosis (Group IV)	Age	Sex	Circulation time (secs.)	Heart rate per minute		Blood pressure mm./Hg.		Mean arterial pressure mm./Hg.		Venous pressure mm./norm. saline	
				Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change
Aortic Stenosis (A.E.)	42	M	>50	88	+4	110/90	−10/0	97	−4	190	−18
Mitral stenosis and insufficiency (R.N.)	31	M	44	82	+2	140/90	−15/−5	107	−9	260	−28
Mitral stenosis and insufficiency (M.R.)	42	F		100	+20	110/80	−20/−20	90	−20	190	−25
Mitral stenosis (L.F.)	44	M	18	80	+4	120/70	−15/−5	87	−9	100	−5
Mitral stenosis and insufficiency + chronic nephritis	56	M	50	76	+20	155/100	−5/−10	118	−10	255	−10
Mitral stenosis (K.Sh.)	48	F	18	88	+4	130/80	−10/−10	97	−10	71	−8

It should be noted that in the first three patients of the last group there was also a decrease of the heart rate, while the fourth did not show any change. In all other cases of congestive heart failure there was an increase in the heart rate (ranging from 2 to 20 a minute), whereas the controls and the hypertensives without heart failure showed no uniform response (Tables I and II).

The effect of full digitalization (1·5 mg. digitoxin) was studied in one case of Group IV and two cases of Group V. In the case of Group IV (A.E.) and one of Group V (P.Ch.), digitalis caused a marked decrease of the venous pressure, while in the third case (Group V, A.J.) it had no

TABLE V

EFFECTS OF PRISCOL IN COR PULMONALE WITH CONGESTIVE HEART FAILURE

Diagnosis (Group V)	Age	Sex	Circulation time (secs.)	Heart rate per minute		Blood pressure mm./Hg.		Mean arterial pressure mm./Hg.		Venous pressure mm./norm. saline	
				Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change	Before priscol	After priscol max. change
Cor pulmonale (H.J.)	65	M	16	96	−4	145/85	−15/−15	105	−15	150	−68
Cor pulmonale and arteriosclerosis (P.Ch.)	61	M	33	84	−10	130/80	−10/−10	97	−10	206	−146
Cor pulmonale and arteriosclerosis (A.J.)	55	M	23	96	−12	110/80	−5/−5	90	− 5	230	−30
Cor pulmonale (M.M.)	48	M	18	100	0	110/80	0/0	90	0	195	−25

effect upon it. The effect of priscol on the venous pressure changed after digitalization: in two cases the decrease was less than before digitalization, while in the third there was no decrease at all (Fig. 1) but rather a slight rise.

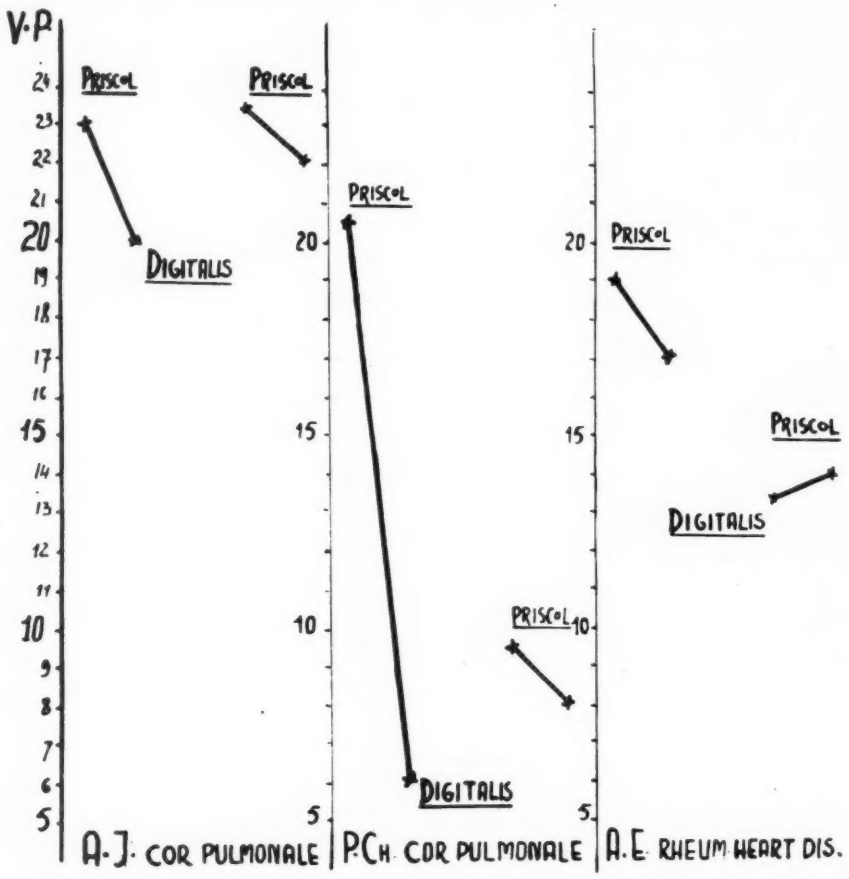

FIG. 1.—The effect of priscol on the venous pressure before and after digitalization. (For details, see text.)

DISCUSSION

The observations of Grimson *et al.* (1948) and Wakim *et al.* (1950) have shown that priscol produces peripheral vasodilatation. This effect has been ascribed to its adrenolytic and sympathicolytic properties. It has been shown that the vasodilating effect of the drug was greatest in the regions where venoconstriction was marked. Since the results of our investigation show a constant drop of the venous pressure in all cases of congestive heart failure, it has to be assumed that in all these cases a functional venoconstriction existed. This assumption is confirmed by the results in normal controls and hypertensives without heart failure. The response of the venous pressure to priscol in these groups was different—the venous pressure rose somewhat in most instances or dropped insignificantly. This different response to the same sympathicolytic drug

indicates a different state of the venous tone preceding injection. These observations suggest that in congestive heart failure an increased sympathetic activity causes venoconstriction, thus participating in the elevation of the venous pressure.

The most pronounced fall of the venous pressure was found in cases of cor pulmonale. This would indicate that venoconstriction in these cases is more pronounced. Since cor pulmonale is always accompanied by anoxia, the rise of venous pressure in this group may be partly related to the decreased oxygen tension of the venous blood and to the accumulation of metabolic products in anoxic tissues. These products may be of an adrenaline-like nature (Raab, 1941), and the marked effect of priscol in these cases could be explained by the counteracting effects of the drug on adrenaline-like substances. (Administration of 100 per cent oxygen in one case of cor pulmonale caused a marked drop of the venous pressure very similar to that observed after priscol.)

The fall in venous pressure after priscol could result from a primary myocardial action of the drug causing an increase of cardiac output and a better emptying of the decompensated heart. In fact a moderate increase of cardiac output has been reported by Siedek (1941). It seems to us, however, that in our cases the action of priscol was mainly peripheral, causing a release of the venoconstriction, since only in one patient with heart failure (Group III, Case LJ) was the drop in the venous pressure associated with a rise of the arterial pressure.

On the other hand the effect on the heart rate was not consistent: in Groups III and IV there was an increase, whilst the first three cases of Group V showed a decrease and the fourth no change at all. Thus, the first three cases of Group V seem to prove most conclusively that the decrease in venous pressure was not mediated through an augmented cardiac output, but through the peripheral action of the drug, since in these cases there was a fall in the heart rate and a drop of the arterial pressure—findings that point clearly to a decrease of the cardiac output.

To study further the influence of the sympathetic nervous system on the venous pressure in congestive heart failure, a cold pressor test (Hines and Brown, 1932) was performed on four patients after the effect of priscol had disappeared, using the opposite arm to that in which the venous pressure was measured. In all instances there was a marked rise of the venous pressure, the average being 25 mm. These results show that sympathetic stimulation (cold pressor test) causes a rise or the venous pressure, probably through venoconstriction. The administration of digitalis in the three cases studied had a varying effect on the venous pressure, in two cases causing a decrease and in the third no change at all. Nevertheless, the response of the venous pressure to priscol after the digitalization was uniformly diminished, suggesting a change in the venomotor tone resulting from digitalis.

Summary

The effects of priscol (a peripherally acting sympathicolytic drug) on the venous pressure were investigated in 22 cases. Five of them were controls without cardiovascular disease and four were cases of hypertension without heart failure; the remainder were patients with congestive heart failure of varying ætiology.

In the patients without congestive heart failure, administration of the drug caused either a small rise of the venous pressure or an insignificant drop. In patients with congestive heart failure there was a constant drop of the venous pressure; this was most pronounced in cases of cor pulmonale. The drop of the venous pressure was almost always accompanied by a fall in the arterial pressure.

It is concluded that priscol lowers the venous pressure in congestive heart failure through its sympathicolytic action on the venous tone.

References

Gollwitzer-Meier, K., and Bohn, H. (1930). *Klin Wschr.*, **9**, 872.
Grimson, K., Reardon, M. J., Marzoni, F. A., and Hendrix, J. P. (1948). *Amer. J. Surg.*, **127**, 968.
Hayward, G. W. (1948). *Lancet*, **1**, 18.
Henderson, Y. (1943). *Medicine*, **22**, 223.

Hines, E. A., and Brown, G. E. (1932). *Proc. Mayo Clin.*, **7**, 332.
Lewis, T., and Landis, E. M. (1930). *Heart*, **15**, 151.
Little, J. M. (1949). *Amer. J. Med.*, **7**, 207.
McMichael, J. (1949). *Ibid.*, **6**, 651.
Meyer, R. T. (1941). *Helvet. med. Acta*, **8**, 18.
Nickerson, M., and Goodman, L. S. (1946). *Fed. Proceed.*, **5**, 161.
Papper, E. M., and Imler, A. E. (1944). *Surgery*, **16**, 402.
Raab, W. (1941). *Arch. interm. Med.*, **68**, 713.
Relman, S. A., and Epstein, F. M. (1949). *Proc. Soc. Exp. Biol., N.Y., Med.*, **70**, 11.
Siedek, H. (1941). *Z. klin. med.*, **139**, 239, cited by Wakim.
Starr, I., Jeffers, W. A., and Meade, R. H., Jr. (1943). *Amer. Heart J.*, **26**, 291.
Wakim, K. G., Peters, G. A., and Horton, B. T. (1950). *J. Lab. Clin. Med.*, **35**, 50.

THE CIRCULATION TIME AS A CLINICAL TEST

BY

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Since Harvey's discovery of the circulation, the velocity of blood flow and its later clinical counterpart, the circulation time, have occupied the thoughts of many workers. The methods used have been as ingenious and diverse as the explanations and hypotheses drawn from them. The result has been that the problem has become more complex and even confused, so that the circulation time as such, has only limited clinical value. Numerous papers that correlate circulation time with other features of cardiac failure have appeared, but their value has been somewhat reduced since many of these other features were but little understood. In view of the more recent work on cardiac output and on the hæmodynamics of the circulation a reinvestigation of circulation time was undertaken.

Although Spier, Wright, and Saylor (1936) recognize the requirements of an ideal substance for estimation of circulation time, such a substance has still to be discovered. Subjective tests have the disadvantage of requiring the intelligent co-operation of the patient. Many of the objective tests involve the peripheral circulation which introduces complications due to the considerable variations in this part of the vascular system. The arrival of tracer substances or concentrated salt solutions at a given point in the circulation may be recognized by objective physical methods, but the apparatus necessary prohibits their routine use. The gasp following the injection of sodium cyanide, 5 to 10 mg. in a 2 per cent solution (Robb and Weiss, 1932) appeared to be a satisfactory objective test. In normals it gave a sharp end point which could be recorded, but in cardiac failure the dose had to be increased to an extent that was considered unsafe. It has been shown by Ruskin and Rockwell (1945) and Robb and Weiss (1934) that suboptimal doses of all substances can prolong the circulation time, as can small volumes of the injected material. However, once the optimal concentration and volume is reached, further additions do not shorten the time. Artificial prolongation of the time was found to occur frequently with sodium cyanide in cardiac failure, because the volume injected was small and the dose used was often found to be minimal.

Methods and Material

The difficulties due to dilution of small doses, were found to be avoided by using saccharine, 2·5 gm. in 4 ml. of sterile water, given rapidly in 1 to 2 sec. through a wide bore needle (Fishberg *et al.*, 1933). This substance was therefore selected for routine circulation time estimations. It gave a constant and satisfactory end point in practically all cases of cardiac failure and was not associated with any unpleasant effects. It was given with the patient in the semi-recumbent position, the arm for injection resting on a pillow at the side of the body. The opposite arm was raised and was dropped by the patient as soon as the sweet taste was appreciated. The only disadvantage of the solution used was occasional local venous thrombosis. Saccharine was used in preference to sodium dehydrocholate, as unpleasant sequelæ have been reported with this substance (Norman, 1947).

In view of the suspected relationship between prolongation of the circulation time and congestive changes in the lungs, vital capacity measurements were made with a portable spirometer. In the

absence of primary lung disease such as emphysema, depression of the vital capacity may be taken as reflecting in some degree the consequences of pulmonary congestion resulting from left-sided heart failure.

Cases selected for study all showed features of cardiac failure in varying degree. Some or all of the following features were present—dyspnœa at rest, raised jugular venous pressure, moist sounds in the lung bases, peripheral œdema, and tender palpable liver. The circulation time and vital capacity were determined as soon as possible after admission, but in a few cases where the condition of the patient was poor, the investigations were necessarily delayed until there was some improvement. The tests were repeated at approximately weekly intervals, the " final " figures being those taken after the clinical evidence of failure had reached its maximum improvement.

Changes in Circulation Time and Vital Capacity before and after Treatment

It was found that the cases could be arranged into three main groups which showed the following features.

Group I. This comprised cases of uncomplicated congestive failure and included cardiac failure due to hypertension, ischæmic heart disease, and chronic rheumatic valvular disease. They showed a prolonged circulation time and reduced vital capacity. After treatment and improvement, the circulation time progressively fell as the vital capacity increased. However, in many of this group the circulation time fell to only a high normal level (Table I). There were three cases in which,

TABLE I

Circulation Time and Vital Capacity in Uncomplicated Congestive Heart Failure before and after Treatment (Group I)

Case	Diagnosis	Before treatment		After treatment	
		Circulation time (sec.)	Vital capacity (litres)	Circulation time (sec.)	Vital capacity (litres)
H.E.	Hypertension	30	1·25	20	2·0
J.H.	Ischæmic heart disease (*a*)	50	2·25	18	3·0
	(*b*)	35	1·75	22	2·25
L.S.	Aortic stenosis	20	0·8	17	1·9
A.C.	Ischæmic heart disease	32	1·0	17	2·15
F.R.	Hypertension	62	1·0	25	1·4
B.T.	Aortic stenosis	23	1·3	15	1·75
T.C.	Hypertension	50	0·8	20	2·0
L.C.	Mitral stenosis and aortic incompetence	40	1·25	18	2·0
S.W.	Hypertension	38	0·75	13	1·6
J.R.	M.S., A.I., T.I.	27	1·5	20	2·2
A.R.	M.S., A.I., T.I.	45	2·0	18	2·2
D.B.	M.S., A.I., T.I.	18	1·8	15	1·8
E.G.	Hypertensive and ischæmic heart disease	45	2·2	23	2·7
M.H.	Coronary occlusion	28	2·75	17	3·25
T.M.	Hypertension	42	1·8	33	2·2

M.S. = Mitral stenosis. A.I. = Aortic incompetence. T.I. = Tricuspid incompetence.

although there was reduction in the circulation time to high normal levels, there was little increase in vital capacity. These were all instances in which tricuspid incompetence or stenosis was present, or in which both were present, in addition to mitral and aortic disease (two cases since confirmed by autopsy). All these patients showed enormous hearts even after improvement, while chest radiographs and cardioscopy were remarkable for the absence of pulmonary congestion.

Group II. Here the patients gave long histories of recurrent and chronic bronchitis and had clinical evidence of emphysema or pulmonary fibrosis. About half were complicated by hyper-

tension. This group showed that although initially there might be some increase in the circulation time there was a marked reduction in the vital capacity. With improvement, the circulation time fell *rapidly* to a low normal value, but the vital capacity showed little or no rise (Table II).

TABLE II

CIRCULATION TIME AND VITAL CAPACITY IN CHRONIC PULMONARY DISEASE BEFORE AND AFTER TREATMENT (GROUP II)

Case	Diagnosis	Before treatment		After treatment	
		Circulation time (sec.)	Vital capacity (litres)	Circulation time (sec.)	Vital capacity (litres)
F.H.	Emphysema	15	0·5	10	1·5
A.D.	Emphysema and hypertension ..	60	1·0	13	1·25
F.B.	Bronchitis, emphysema, and hypertension.	27	1·1	12	1·2
W.G.	Chronic bronchitis and hypertension..	20	0·5	10	0·6
A.S.	Bronchitis and ischæmic heart disease	14	2·2	11	2·25
A.G.	Pulmonary fibrosis	13	1·65	13	1·70
A.F.	Emphysema and bronchitis	19	1·1	14	1·5
W.H.	Emphysema (severe) and bronchitis ..	15	0·5	10	1·5
E.O.	Hypertension, bronchitis, and anæmia	12	1·0	11	1·25

Group III. In this group, there were four cases of acute glomerular nephritis of which three showed some initial mild hypertension, a patient with acute rheumatism whose chest X-ray was compatible with " rheumatic pneumonia," and a case of acute uræmia following anuria due to a concealed accidental hæmorrhage, with subsequent recovery after Cæsarian section.

The circulation time was normal or only slightly prolonged; the vital capacity was, however, reduced in all cases. With improvement the circulation time remained normal, or in one in which it was raised, rapidly became normal. The vital capacity rose to its presumed previous level (Table III).

TABLE III

CIRCULATION TIME AND VITAL CAPACITY IN MISCELLANEOUS CIRCULATORY DISORDERS BEFORE AND AFTER TREATMENT

Case	Diagnosis	Before Treatment		After Treatment	
		Circulation time (sec.)	Vital capacity (litres)	Circulation time (sec.)	Vital capacity (litres)
A.K.	Acute nephritis	25	1·5	15	3·0
L.S.	Acute rheumatic lung	12	1·2	10	2·5
W.B.	Acute nephritis	15	2·5	15	3·75
D.M.	Acute nephritis	17	1·7	15	2·5
A.B.	Uræmic lung	13	1·25	13	2·25
M.S.	Acute nephritis	12	2·5	12	3·75

These cases consisted mainly of previously healthy young adults who presented with dyspnœa, some rise in jugular venous pressure, and X-ray appearances similar to those of pulmonary venous congestion.

Changes in Heart Size and Circulation Time

Changes in heart size were determined by comparison of the ratio $\frac{\text{Transverse diameter of heart}}{\text{Internal diameter of chest}}$ during failure and later during improvement. The transverse diameter of the heart was taken as the sum of the distances from the mid-line to the outermost right and left borders of the heart. The internal diameter of the chest was measured at the level of the fourth costochondral junction. All measurements were in centimetres and were taken from teleroentgenograms. The upper limit of normal for this ratio has been taken as 0·54 (Meneely and Chesnut, 1947).

It can be seen that considerable reduction in the arm to tongue circulation time can occur with little change in the cardiothoracic ratio (Table IV). Although this ratio may remain much higher than the accepted normal, the circulation time may be within normal limits.

TABLE IV

Changes in Heart Size and Circulation Time Resulting from Treatment of Heart Failure

Case	In failure			After treatment		
	Trans. diam. heart / Trans. diam. chest	Ratio	Circulation time (sec.)	Trans. diam. heart / Trans. diam. chest	Ratio	Circulation time (sec.)
S.W.	16 cm. / 24 cm.	0·66	38	14 cm. / 23 cm.	0·61	13
L.C.	15·25 / 25·75	0·59	40	15·25 / 25·5	0·59	18
T.C.	16·5 / 24	0·66	50	16·5 / 25	0·65	20
F.R.	18 / 24	0·75	62	16 / 23	0·70	25
A.C.	17 / 24·5	0·69	32	17 / 24	0·64	17
J.H.	18 / 25	0·72	50	17 / 25	0·68	18
J.H.	19·3 / 25·2	0·76	35	19·4 / 25·2	0·76	22
D.B.	18 / 22·5	0·80	17	18 / 22·5	0·80	15
B.T.	11 / 22·5	0·49	23	11 / 22	0·50	15

Comparison of Arm–Tongue and Heart–Tongue Times and of the Circulation Time with the Minute Cardiac Output

Opportunity was taken in cases being investigated by cardiac catheterization to compare the arm to tongue circulation time with that of the heart to tongue time. The latter was determined by injecting the saccharine solution through the cardiac catheter into the right auricle and noting the time required to appreciate the taste. In 11 cases so investigated it was found that the difference

between the arm to tongue, and the right heart to tongue times varied between 3 to 6 sec. and was not related to the right auricular pressure measured by means of a saline manometer.

In 18 cases the minute cardiac output was determined by the Fick principle and compared with the arm to tongue circulation time. It appears that with normal circulation times the minute cardiac output is higher than in those cases where the circulation time is prolonged (Table V and Fig. 1).

TABLE V

RELATIONSHIP BETWEEN CIRCULATION TIME AND CARDIAC OUTPUT

1. Normal circulation time			2. Prolonged circulation time		
	Circulation time (sec.)	Cardiac output l/m.		Circulation time (sec.)	Cardiac output l/m.
Emphysema and chronic cor pulmonale.	16	7·4	Bronchitis and hypertension	23	7·5
Acute nephritis	18	5·8	M.S. and A.I.	40	1·75
A.I. and myxœdema	17	5·0	Ischæmic heart disease ..	50	3·1
M.S. (compensated)	14	7·2	Hypertensive heart disease ..	38	4·6
Cor pulmonale..	13	6·4	Hypertension and emphysema	27	2·2
Mitral stenosis and anæmia ..	15	5·2	Hypertension and ischæmic heart disease.	40	2·8
Emphysema, bronchitis, cor pulmonale.	16	10·0	Malignant hypertension ..	26	2·1
Emphysema and polycythæmia	15	3·8	Rh. heart disease, M.S., and A.I.	43	2·8
Acute nephritis	15	7·2	A.I., M.S., and T.I.	25	1·9

M.S. = Mitral stenosis. A.I. = Aortic incompetence. T.I. = Tricuspid incompetence.

The circulation time determined by the usual technique may be affected by delay in the venous return to the heart, in the arterial channel, and finally in the appreciation of the taste sensation itself. From the above it appears that delay on the venous side even when the venous pressure is much raised, probably plays only a small part in the prolongation of the circulation time. Delay on the arterial side and in the appreciation of the taste must also be but a small factor with marked prolongation of the circulation time. The longer times in elderly patients, noted by many workers, may be due to delay in taste perception. For these reasons the normal range for saccharine circulation time was extended up to 18 sec.

DISCUSSION

Much prolongation of the circulation time has usually been accepted as being indicative of congestive heart failure of whatever ætiology (Tarr, Oppenheimer, and Sage, 1932). Blumgart and Weiss (1928) regarded the pulmonary circuit as the main site of delay in the velocity of the blood flow. They state, that in cardiovascular disease there is a striking tendency for a decrease in vital capacity of the lungs to be associated with an increase in the pulmonary circulation time, denoting a slower speed of blood flow through the lungs. Of more recent years, Gernandt and Nylin (1946) and Nylin (1945) have studied the volume of, and changes in, the residual blood of the heart and the dilution curve of activity in arterial blood after intravenous injection of radioactively labelled corpuscles. They showed statistically a correlation between heart volume, i.e. the amount of residual

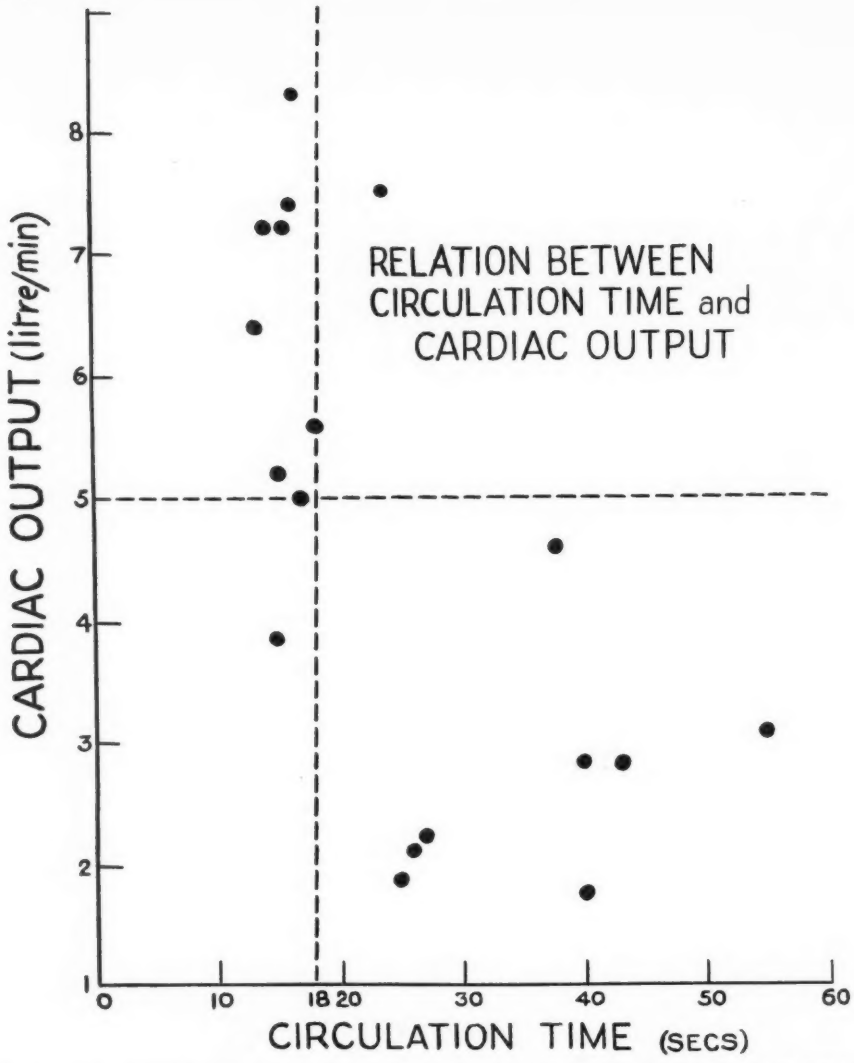

FIG. 1.—The relation between the cardiac output and the arm to tongue circulation time in 18 patients.

blood, and the circulation time (correlation coefficient, 0·51). The greater the residual blood the longer the delay in the heart, and thus the longer will the test substance take to reach the taste buds. Nathanson and Elek (1947) also found a statistically significant correlation between heart size and circulation time. Meneely and Chesnut (1947), however, conclude that the circulation time is proportional to the relative heart volume in patients with heart disease—not to residual blood which is an expression of dilution. They do not agree that the residual blood delays the circulation time but believe that there is associated impaired myocardial function.

In emphysema and other causes of chronic pulmonary insufficiency it is generally agreed that the circulation time (arm to tongue) is normal (Blumgart, 1931; Oppenheimer and Hitzig, 1936; Gross, 1945) even when associated with right ventricular enlargement. Prolongation of the circulation time in these conditions is taken as being indicative of complicating myocardial failure (Gillanders, 1949). However, Taquini *et al.* (1948) observed that severe pulmonary emphysema and fibrosis with pronounced polycythæmia, resulted in prolonged circulation time when no heart failure was present. In our experience polycythæmia is an unusual complication of pulmonary fibrosis and emphysema, and in one case (W.H., Table II) who showed marked polycythæmia with a twice normal blood viscosity (*in vitro*), there was a rapid circulation time throughout his stay in hospital.

The data presented indicate that the factors involved are probably complicated and may vary from case to case. These factors may be dilatation of the cardiac chambers, the volume of the pulmonary vascular bed, and the cardiac output especially in relation to these relative volumes. An increase in either the cardiac volume or in the pulmonary vascular bed might be compensated by an increase in cardiac output, so that the resultant circulation time may be unchanged and conversely a diminution of the cardiac output, with no change in the pulmonary vascular bed, would prolong the circulation time.

In Group I there was an apparent relationship between the shortening circulation time and increasing vital capacity. The cardiac output was variable but usually low. Amongst this group were instances in which there was no radiological evidence of cardiac enlargement even when in failure, and others in which although the heart was large even after improvement, there was a normal circulation time. In some cases of cardiac enlargement serial X-rays showed little measurable reduction after improvement. Prolonged circulation times have been noted by others without great cardiac enlargement (Gross, 1945). Although with improvement there was a progressive increase in vital capacity with a corresponding diminution in the circulation time, the tendency in this group was to have a circulation time that was on the high side of normal even after clinical evidence of failure had subsided.

The cases in Group II had as a common basic feature chronic lung disease, which in itself was primarily responsible for the diminished vital capacity. When heart failure develops, pulmonary capillary congestion is not a necessary accompaniment, as rising pulmonary arterial pressure is the main cause of the strain (Cournand, 1947). The insignificant change in vital capacity is therefore to be expected. The circulation time is frequently within normal limits and in keeping with the observation that the cardiac output in such patients tends to be normal or raised (Richards, 1945; Stead *et al.*, 1948). In gross failure, however, in such patients, the circulation time may be prolonged, and it has been shown that in advanced failure the minute cardiac output may fall to low levels (Howarth *et al.*, 1947).

Group III consists of cases who showed a special variety of pulmonary congestion occurring par excellence in uræmia with hypertension, but also in acute nephritis and acute cardiac rheumatism. It is peculiar in its radiological, histological, and clinical features (Doniach, 1947). Dyspnœa may be much less intense than in other comparable types of pulmonary congestion due to cardiac causes. The mechanism at work in the production of these cases is obscure and these circulation time studies merely serve to point out a further difference from more ordinary types of pulmonary congestion.

It has been shown that delay in the circulation time can occur with normal sized hearts, and conversely there may be no delay with grossly enlarged hearts. Although this does not exclude cardiac dilatation as a factor in causing delay, it is unlikely to be the main one. It appears more probable that the major portion of circulation time is occupied in passage through the pulmonary vasculature. The mean pulmonary circulation time is dependent on the relationship between the cardiac output and the volume of the pulmonary vascular bed. In the various conditions, changes in either may predominate or both play some part. Thus, left ventricular failure may lead to pulmonary congestion, and so both factors would tend to prolong the circulation time. It is in these conditions (Group I) that the greatest prolongation occurred. The accompanying reduction in the vital capacity in this group suggests the presence of an increase in the pulmonary vascular

bed, but other factors such as œdema, hydrothorax and cardiac enlargement may also play some part in reducing the vital capacity.

In Group II there is no marked prolongation in circulation time until the previously high cardiac output falls and it is probable that this fall in minute cardiac output is the main cause for any prolongation. Thus, there is no increase in the arm to tongue time until the heart fails to maintain the high output initially demanded by the respiratory disability.

The special pulmonary congestion seen in Group III may only initially show an increase in the circulation time, which rapidly returns to normal. Although the cause of this is not quite clear, it is possibly connected with some transient increase in pulmonary vascular pressure which together with some pulmonary capillary dysfunction gives rise to a highly fibrinous alveolar transudate and special radiological appearances (Doniach, 1947).

Summary

The circulation time using saccharine solution and the vital capacity have been estimated in cases presenting features of congestive cardiac failure and have been repeated during recovery.

Our patients could be divided into three groups depending on the changes that occurred in the circulation time and vital capacity.

These groups consisted of (i) instances of uncomplicated congestive cardiac failure; (ii) cases complicated by chronic respiratory disease; and (iii) a special group typically seen in acute nephritis and uræmia.

Comparison of the circulation time with the cardiac output and the heart size has been made. The parts played by the cardiac output, cardiac size, pulmonary vascular bed, and pulmonary œdema have been discussed in relation to the changes occurring in these groups.

It is emphasized that all these factors must be taken into account to determine the significance of the circulation time. Serial readings of the circulation time and the vital capacity by differentiating cases into the groups described help to evaluate the relative parts played by these factors and their underlying cause.

I should like to express my gratitude to Professor John McMichael for his help and advice in preparing this paper.

References

Blumgart, H. L. (1931). *Medicine*, **10**, 1.
——, and Weiss, S. (1928). *J. Clin. Invest.*, **5**, 379.
Cournand, A. (1947). *New York Acad. Med.*, **23**, 27.
Doniach, I. (1947). *Amer. J. Roentgenol.*, **58**, 620.
Fishberg, A. M., Hitzig, W. M., and King, F. H. (1933). *Proc. Soc. Exper. Biol. & Med.*, **30**, 651.
Gernandt, B., and Nylin, G. (1946). *Amer. Heart J.*, **32**, 411.
Gillanders, A. D. (1949). *Quart. J. Med.*, **18**, 263.
Gross, D. (1945). *Amer. Heart J.*, **30**, 19.
Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1947). *Clin. Sci.*, **6**, 187.
Meneely, G. R., and Chesnut, J. L. (1947). *Amer. Heart J.*, **33**, 175.
Nathanson, M. H., and Elek, S. R. (1947). *Ibid.*, **33**, 464.
Norman, J. K. (1947). *Ibid.*, **34**, 740.
Nylin, G. (1943). *Ibid.*, **25**, 598.
—— (1945). *Ibid.*, **30**, 1.
Oppenheimer, B. S., and Hitzig, W. M. (1936). *Ibid.*, **12**, 257.
Richards, D. W., Jr. (1945). *Federation Proc.*, **4**, 215.
Robb, G. P., and Weiss, S. (1932). *Amer. Heart J.*, **8**, 650.
——, —— (1934). *Ibid.*, **9**, 742.
Ruskin, A., and Rockwell, P. (1945). *Proc. Soc. Exper. Biol. & Med.*, **60**, 40.
Spier, L. C., Wright, I. S., and Saylor, L. (1936). *Amer. Heart J.*, **12**, 511.
Stead, E. A., Warren, J. V., and Brannon, E. S. (1948). *Arch. intern. Med.*, **81**, 282.
Taquini, A. C., Fasciolo, J. C., and Savrig, T. R. E. (1948). *Ibid.*, **82**, 535.
Tarr, L., Oppenheimer, B. S., and Sage, R. V. (1932). *Amer. Heart J.*, **8**, 766.

ELECTROCARDIOGRAPHIC CHANGES IN CHRONIC COR PULMONALE

BY

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Electrocardiographic abnormalities have long been noted in cases of heart failure due to chronic cor pulmonale but there has been much discussion about their diagnostic importance and their causation. This paper is a study of a small series of cases of well established chronic cor pulmonale with congestive heart failure, in an attempt to determine the typical cardiographic pattern and to distinguish, if possible, changes due to abnormality of the heart from changes due to its altered position in the thorax.

History. Einthoven in 1906 noted that deep S waves in lead I and tall R waves in lead III may accompany hypertrophy of the right ventricle. He also noted that changes in the position of the heart in relation to the chest would alter the electrocardiographic appearances. Hermann and Wilson (1922) and Cohn and Raisbeck (1922) made extensive studies of the effect of the position of the heart and of the changes in ventricular hypertrophy, and Lewis (1925) agreed with their conclusions that both rotation of the heart and lesions of conduction might produce the appearance of ventricular preponderance in the cardiogram. Barnes and Whitten (1929) noted depression of the S–T segment and inversion of T waves in leads II and III which they stated accompanied right axis deviation in the typical tracing in cases of right ventricular hypertrophy. Wood and Selzer (1939) used pectoral as well as limb leads in the study of right ventricular hypertrophy and reported among their findings those of six cases of chronic cor pulmonale and five cases of acute cor pulmonale due to pulmonary embolism.

Since the introduction of unipolar lead electrocardiography by Wilson and his colleagues (Wilson *et al.*, 1944; Goldberger, 1949) much more information has been gained about the effects of alterations in the position of the heart, and it is often possible to separate the effects of ventricular hypertrophy from those of positional changes. In chronic cor pulmonale, however, the heart is often rather vertical with clockwise rotation, due presumably to the emphysema which is often the underlying chest condition. The cardiographic result of the change in position is often a tracing resembling that commonly accepted as being due to right ventricular hypertrophy, namely, marked right axis deviation with, in some cases, depression of S–T and inversion of T in leads II and III (Barnes and Whitten, 1929). Identical tracings have, however, been noted to occur in the absence of right ventricular hypertrophy (Myers *et al.*, 1948). Hence it is of the greatest importance in cases where emphysema is associated with heart failure to identify any cardiographic changes that will indicate right ventricular hypertrophy or any other functional change in the right ventricle or auricle in the presence of the pattern of the vertical clockwise-rotated heart.

METHOD

The electrocardiographic data of 20 cases of well established chronic cor pulmonale diagnosed clinically were studied in detail. The criteria of diagnosis were as follows: in all, there was on admission gross peripheral œdema, raised jugular venous pressure, hepatomegaly, and gross cyanosis.

There was in all, a long-standing history of chronic cough and breathlessness, and no case was included where there was hypertension or a history of rheumatic fever or signs of rheumatic heart disease such as mitral or aortic diastolic murmurs or an aortic systolic murmur or possible congenital heart disease.

In many cases, on admission a severe broncho-pneumonia complicated the primary chest condition. Four of the patients have died since the investigation started, and in the three where post-mortem examination was obtained it confirmed the diagnosis and showed both the expected primary lung condition and right ventricular hypertrophy and an absence of any other lesion except, in two cases, slight thickening of the left ventricle also.

Electrocardiograms were taken on admission and in many cases were repeated at intervals for many months. The leads routinely recorded were the standard bipolar limb leads I, II and III, unipolar limb leads aVR, aVF, and aVL (Goldberger, 1949) and unipolar chest leads V1 to V6. Later, lead V3R was added to the routine list, being recorded from the right pectoral region in a position equivalent to that of V3, from the left. In some cases unipolar leads were taken circumferentially around the chest and in some cases simultaneous records were made of leads VR (Wilson), V1 and V6 and of V3R, V1 and V6 using the Elmquist triplex electrocardiograph. The records were all uniformly standardized (1 mv. = 1 cm.) and a standardization curve was recorded at the time so that adjustments could be made in measurement where necessary.

In many of the cases, records were made of the mean right auricular and right ventricular pressures recorded with a saline manometer after cardiac catheterization.

Results and Discussion

The cardiographic findings on admission in the 20 cases studied are summarized in order to give data comparable with those previously published. As the analyses of the authors quoted are not in a comparable form it is necessary to present two separate tables. Table I shows the analysis of the findings by the criteria used by Myers *et al.* (1938) in the cardiographic diagnosis of right ventricular hypertrophy in 40 cases in which autopsy confirmation was obtained, and a comparable analysis of the present series. Table II shows a comparison of the incidence of cardiographic signs in these 20 cases with that given by Wood (1948) in his series of 100 cases of chronic cor pulmonale.

TABLE I

Diagnostic Findings in 20 Cases of Chronic Cor Pulmonale compared with 40 Cases of Right Ventricular Hypertrophy (Myers *et al.*, 1948)

Electrocardiographic criteria on which diagnosis of right ventricular hypertrophy was made	Series of Myers *et al.* (1938) (percentage in 40 cases)	This series (percentage in 20 cases)
Reversal of R/S ratio in lead I, deep S in V6, delayed intrinsic deflection in V1 (to 0·03–0·05 seconds), tendency to small Q in V1, to inverted T in V1, and to upright T in V6, QRS less than 0·12 seconds, absence of notching of R in V1	32·5	25
Incomplete right branch bundle block (intrinsic deflection 0·05–0·075 seconds after start of QRS in the right præcordial leads but QRS less than 0·12 seconds)	22·5	20
Signs of right ventricular hypertrophy or incomplete right branch bundle block in V3R but not in V1 or V2	5·0	10 *
Complete right branch bundle block	7·5	0
Large R in aVR with deep S in V6 (R twice Q or more in aVR)	15·0	25
Signs not diagnostic	17·5	20

* V3R recorded in 11 cases only, two of which showed this finding.

TABLE II

ELECTROCARDIOGRAPHIC SIGNS IN 20 CASES OF CHRONIC COR PULMONALE COMPARED WITH THE FINDINGS OF WOOD (1948) IN 100 CASES

Electrocardiographic signs in chronic cor pulmonale	Series of Wood (1948) (percentage in 100 cases)	This series (percentage in 20 cases)
P pulmonale	85	60
Complete right branch bundle block	4	0
Right axis deviation	46	85*
Tendency to right axis deviation	11	5
Deep S in all bipolar limb leads	9	20
Low voltage	40	15
Inversion of T in V1 to V3	13	85
Fixed R/S pattern in V1 to V5 with S dominant	16	40
Upright QRS in V1 with a conspicuous S in V5	16	25

* In 30 per cent there was marked right axis deviation with depression of S-T and inversion of T in II and III.

It will be noted that 60 per cent of the cases showed the P pulmonale, a sharply peaked P wave of 2·5 mm. or more in height in the standard leads or of 3 mm. or more in the chest leads, and that this finding compares with that of Wood in being most significant. Myers *et al.* (1948) and Zuckermann *et al.* (1948) postulated that this tall P wave could be natural when there was a low vertical heart, but Wood (1948) stated that it was never seen in normal vertical hearts.

Inversion of T in V1, V2, and V3 was present in 85 per cent, whereas this sign was not prominent in the cases described by Wood (1948). The frequency of this finding may have been related to the advanced nature of the cases selected for study. Nearly all showed right axis deviation and 30 per cent showed the pattern described by Barnes and Whitten (1929), with depression of S–T and inversion of T II and T III.

The pattern described by Myers and his colleagues (1948) consisting of reversal of the R/S ratio in V1, a deep S in V6, delay of the intrinsic deflection in V1 to 0·03–0·05 sec., with a tendency to a small Q in V1, to inversion of T in V1, and an upright T in V6, but with a total QRS time less than 0·12 sec. and without notching of R in V1, was seen in 25 per cent of the cases, a figure comparable to that given by Myers. Fig. 1 shows an example of this type of tracing. Wood (1948) stated that 16 per cent of his cases showed a chiefly upright QRS in V1 with a conspicuous S wave in V6. Complete right branch bundle block was not seen in any of the tracings taken on admission but developed some three months later in one patient. Incomplete right branch bundle block (delay of the intrinsic deflection of V1 or V3R to 0·05–0·075 sec. with a total QRS time of 0·12 sec. or less) had not previously been observed in this patient. Incomplete right branch bundle block was noted in the right præcordial leads in four (20%) of the cases, and Fig. 2 shows such a tracing. Incomplete right branch bundle block was seen in V3R in one patient when it was not present in V1 or V2 and conduction delay was present in one other case in V3R but not in V1 or V2 (delay of the intrinsic deflection to 0·03–0·05 sec., Myers *et al.*, 1948, and Wilson *et al.*, 1947). If V3R had been recorded in the earlier cases it is likely that some at least would have shown abnormal conduction here.

There was a significant late R wave in aVR in all the 20 cases. In 25 per cent, R in aVR was at least twice the size of S and there was a deep S wave in V5. This had been a diagnostic feature in 15 per cent of the cases of Myers *et al.* (1948). The QR pattern in aVR is described by Goldberger (1949), who considered that it occurred in marked clockwise rotation of the heart with backward rotation of the apex, the tall R wave being a reflection of the termination of the spread of the impulse through the epicardial portion of the left ventricular wall at the back of the heart. He noted also that a very tall R wave in aVR (more than twice the size of the Q wave) might occur in right ventricular hypertrophy. Myers *et al.* (1948) gave considerable attention to the presence of the R wave

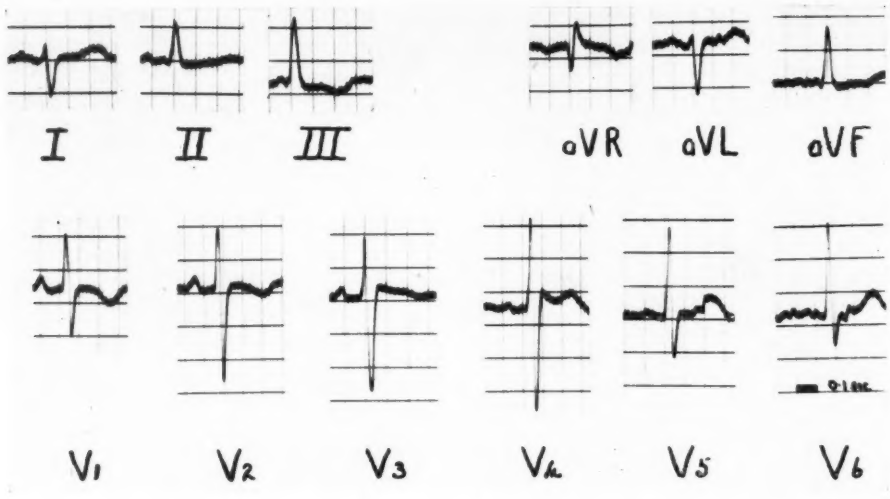

FIG. 1.—Electrocardiogram in a case of chronic cor pulmonale showing the large R wave in the right-sided chest leads and in aVR, a significant S in V6, and inversion of T in all the chest leads to the right of V4.

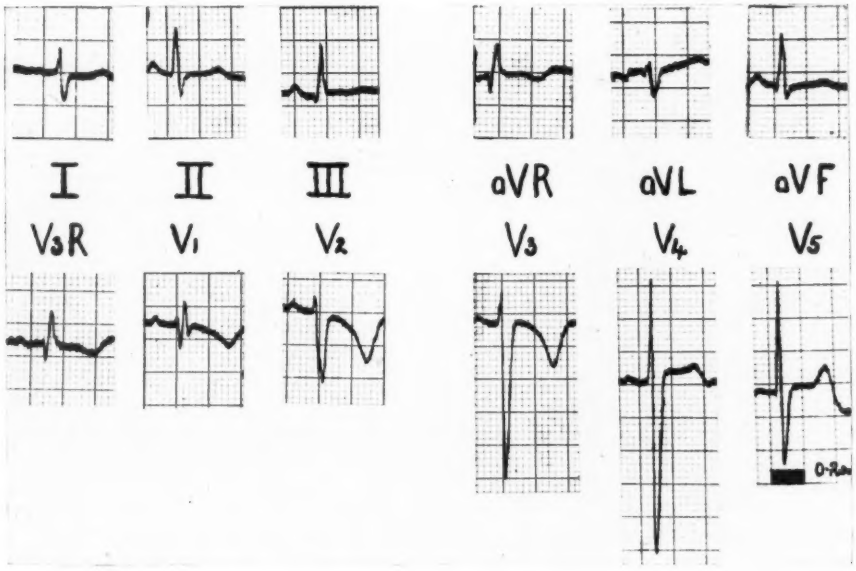

FIG. 2.—Electrocardiogram in a case of chronic cor pulmonale showing incomplete right branch bundle bloc[illegible] the large late R in aVR, V3R, and V1, a significant S in V5, and inversion of T in the chest leads to the right of [illegible]4.

in aVR in right ventricular hypertrophy but agreed with Goldberger that this wave was produced by the left ventricle and was due to the rotation of the heart. Schlesinger *et al.* (1949) showed by intracardiac and œsophageal leads that aVR showed an R wave in right ventricular hypertrophy which they suggested was probably due to late activation of the right ventricular wall and the observations of Sodi-Pallares *et al.* (1947) seem to agree with this concept. Hecht (1946) had shown by intracardiac leads that in right branch bundle block VR resembled the high intra-auricular leads and might show a small Q and a large slow R, as the cavity potential in right branch bundle block was at first negative on the left, then finally positive on the right.

In the 20 cases observed, the R wave in aVR was relatively small in two only (1/4 of the Q wave), but in most the R wave was the striking feature, being usually twice or three times larger than the Q wave and in two cases five and six times the size.

The position of the heart was analysed by the criteria of Goldberger (1949). In only one case was there a horizontal heart and this was associated with marked clockwise rotation and forward rotation of the apex; here the R wave was only half the size of the Q wave in aVR. In 19 cases the heart was vertical, in six with moderate and in 13 with marked clockwise rotation (moderate when R equalled S in size in V4 or V5 and marked when the transition point lay beyond V5). The R wave in aVR tended to be higher when marked clockwise rotation was present. There was, however, no correlation between the height of the R wave in aVR and the presence or absence of backward rotation of the apex which was almost evenly distributed among the 19 vertical hearts and there was no correlation between the presence or absence of P pulmonale and the height of R in aVR.

In order to determine the source of the large R wave in the right arm lead records were made of VR, V1, and V6 simultaneously, and also of V3R, V1, and V6 simultaneously in nine cases, and in six of these multiple leads were taken circumferentially around the chest. Where V3R showed an R wave this R wave was synchronous with the R of VR. In all nine cases examined the R of VR and of V3R was synchronous with the R of V1 and occurred much later than the R of V6. Fig. 3

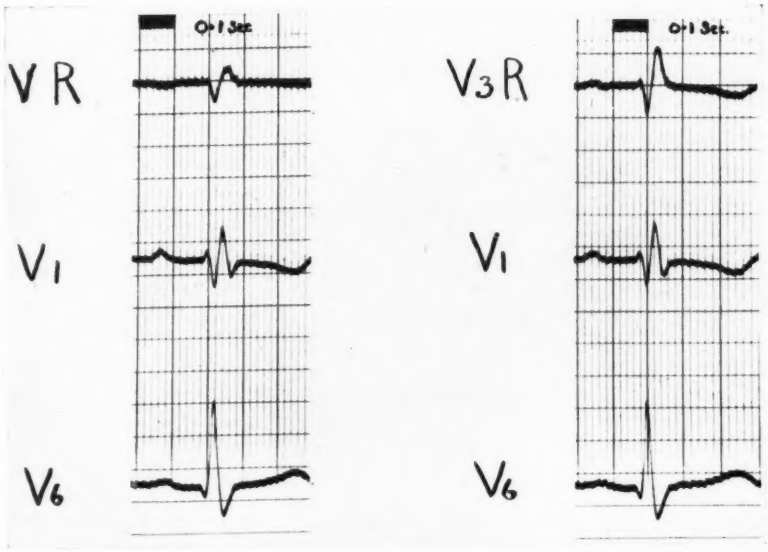

FIG. 3.—Electrocardiogram in a case of chronic cor pulmonale showing simultaneous records of VR, V1, and V6; and of V3R, V1, and V6. R in VR and V3R corresponds to R in V1, but is significantly later than R in V6.

shows the type of tracing obtained. In the six cases in which circumferential chest leads were available five showed that the R wave in aVR was unlikely to be a reflection of left ventricular excitation because the R wave of V6 became progressively smaller when the exploring electrode moved to the left and was almost absent over the spine or in the right posterior chest leads while there was still an appreciable R in the anterior right chest leads and in lead aVR. Fig. 4 illustrates this finding diagrammatically. In the remaining case the left ventricular R wave persisted in the posterior chest leads and merged with the R wave from the anterior right chest. Here the R in VR was only slightly delayed in time from the R of V6 so that the R in VR may have had a composite origin, both from

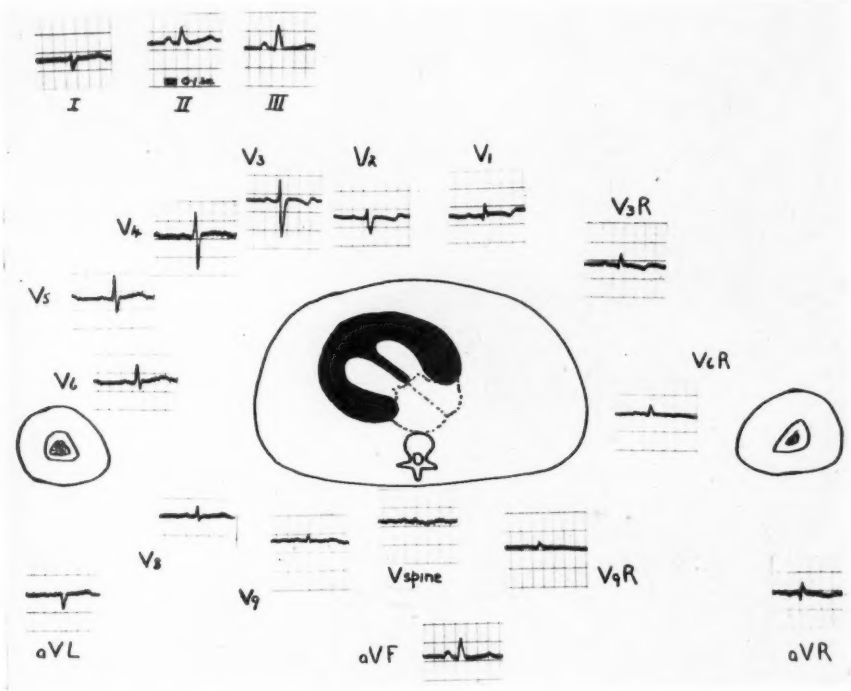

FIG. 4.—Electrocardiogram in a case of chronic cor pulmonale showing diagrammatically a horizontal cross-section of chest and arms at about the fourth costal cartilage. Each unipolar lead tracing is mounted opposite the site of the exploring electrode. Note the delayed R in V1, V3R, V6R, and aVR, and the absence of the left ventricular R wave in V spine suggesting that the R wave in aVR is related more to right than to left ventricular excitation.

the left and right ventricular walls as is suggested by Myers *et al.* (1948). The large late R wave in aVR and in V3R seems likely therefore to be related in most cases of chronic cor pulmonale without complete right branch bundle block to right ventricular excitation, probably to the final spread of the impulse outward through the thickened right ventricular wall.

A cardiographic diagnosis of chronic cor pulmonale could be made in 19 of the 20 cases examined. In 12 there was a well marked P pulmonale, and a further 3 showed the common pattern described by Myers *et al.* (1948) in right ventricular hypertrophy. One further case showed incomplete branch bundle block in V3R but not in V1 or V2 and one more showed conduction delay in V3R only. In two others there was a large R in aVR and a deep S in V6. In one of these two, V3R also showed a

large R but the intrinsic deflection was not delayed and in the other no V3R was available. In the remaining case the tracing was not diagnostic, showing only rather low voltage curves, right axis deviation, a vertical heart with moderate clockwise rotation, and a small R in aVR only half the size of the Q wave; no V3R was taken: this case came to necropsy and showed well marked right ventricular hypertrophy and dilatation, very slight left ventricular hypertrophy, and chronic pulmonary fibrosis due to lipoid pneumonia.

In 13 of the 20 cases serial electrocardiograms are available; none of these 13 had taken any digitalis for at least a month before admission. Nine of the 13 cases showed considerable improvement in the pattern coincident with improvement in the clinical condition. The changes noted included improvement in the P wave in 5 and decrease in the extent of T wave inversion in the chest leads in 8 cases. The P wave in several cases decreased from a sharply peaked wave of well over 3 mm. in height to a pattern that was not in any way abnormal although in one the typical P pulmonale became converted into a low flat P of 0·12 sec. in duration and only 1·5 mm. in height. Improvement in the clinical state was associated in one case, to be described in more detail later, with reversal of the inverted T waves in V1 to V4 to a normal upright pattern in a little over a month, and with loss of the P pulmonale pattern six weeks later. In two of the three cases where the P wave became normal with clinical improvement, no change in the cardiographic position of the heart was seen in later tracings suggesting that the abnormality of the P wave was not due to a positional change of the heart. In two cases inversion of T in V1 to V4 became reduced to inversion in V1 and V2 only and in four others inversion of V1, V2, and V3 was converted to an upright pattern in all three leads in from two to six months while in one further case inversion of T in V1, V2, and V3 was reduced to inversion in V1 and V2 only after a period of five months.

All these records were analysed in terms of Goldberger's criteria (1949) for the position of the heart but in 8 of the 9 cases where this striking cardiographic improvement occurred no change in the position of the heart was found. In the case mentioned above, where clinical improvement was associated with a quick return to normal of the inverted T waves in V1 to V4 and a later return to normal of the P wave, the position of the heart remained vertical with backward rotation of the apex but clockwise rotation, which was marked on admission, was only moderate a month later and disappeared in the next month. The extent and rapidity of the clinical recovery in this case was remarkable. Although his history and physical signs were those of chronic cor pulmonale with congestive failure of two months' duration the progress suggested that there had been a super added acute cor pulmonale. The possibility that there had been pulmonary embolism could not be excluded with certainty.

In five cases that showed, on admission, delay in conduction in the right sided chest leads or incomplete right branch bundle block no improvement was shown in conduction in later tracings even though improvement occurred in the inversion of the T waves of the right-sided chest leads in all. In two further cases incomplete right branch bundle block appeared for the first time in subsequent tracings, and in one of these coincided with the reversal of previously inverted T waves in V1, V2, and V3. In another complete right branch bundle block developed four months after the original tracing had been taken and while the clinical state remained considerably improved.

These observations suggest that the conduction delay so commonly observed in the right-sided chest leads and the signs of right ventricular hypertrophy have a separate origin from the T wave inversion of these leads. The term " right ventricular strain " has been used by various workers with varying implications (Wilson *et al.*, 1947; Katz, 1946; Katz and Wenstein, 1947; Goldberger, 1949). In view of the reversible nature of the inversion of the T wave in the right-sided chest leads in chronic cor pulmonale and the doubt as to the cause of this pattern it seems that " right ventricular strain " is a term best reserved exclusively to describe this inverted T pattern and this definition will be followed in the following discussion.

Temporary inversion of the T wave in the right-sided chest leads often occurs in acute pulmonary embolism where it is not necessarily associated with right ventricular hypertrophy (Wood and Selzer, 1939). In the cases of chronic cor pulmonale described here there is no reason to suppose that right ventricular hypertrophy has been in any way reduced, yet the inverted T waves became

upright, suggesting that the pattern of right ventricular strain was not dependent upon right ventricular hypertrophy. A similar conclusion with regard to the inverted T waves of the left-sided chest leads in essential hypertension may be made from the observation by White *et al.* (1945) that after sympathectomy the appearances of left ventricular strain may disappear in some cases without any decrease in the size of the heart radiologically or in the level of the peripheral blood pressure. Zuckermann *et al.* (1948) suggested that the right ventricular strain pattern is due to a change in rotation of the heart towards a more juvenile position, but the observations recorded here suggest that it is not necessarily dependent on a change in cardiac position in chronic cor pulmonale. Goldberger (1949) also drew an analogy between right ventricular strain and the juvenile pattern, but did no more than suggest that the potassium metabolism might be altered in both cases.

Mean right intracardiac pressures measured by saline manometry after cardiac catheterization in 12 cases of chronic cor pulmonale are shown in Table III with an analysis of the cardiographic findings at the time the observations were made. There was no relation between either auricular or

TABLE III

ELECTROCARDIOGRAPHIC APPEARANCES AND FINDINGS IN CHRONIC COR PULMONALE AND LEVELS OF RIGHT AURICULAR AND VENTRICULAR PRESSURE

Patient	Electrocardiographic findings				Mean pressures in cm. of saline above sternal angle	
	P pulmonale	Right ventricular strain. Inversion of T in V1–V4 = +++ V1–V3 = ++ V1–V2 = +	Right bundle branch conduction delay. Intrinsic deflection. V1 or V3R. 0·03–0·05 sec. = + 0·05–0·075 sec. = ++	Right ventricular hypertrophy	Right atrium	Right ventricle
Bra.	0	++	0	+	+ 19·0	+ 48·0
Bo.	0	+++	+	+	+ 10·0	+ 45·0
Sm.	0	++	+	+	..	+ 44·5
St.	0	0	+	+	+14·0	+ 39·0
Sh.	0	0	0	0	+ 15·5	+ 34·5
Ro.	+	+++	+	+	− 1·0	+ 29·0
Wr.	+	++	0	+	+ 2·5	+ 24·0
Ca.	0	+++	++	+	..	+ 22·0
Hudg.	0	+++	0	+	− 7·0	+ 20·0
Huds.	0	++	0	+	− 6·5	..
Ne.	+	0	0	+	+ 2·5	..
Bri.	0	..	..	..	+ 7·0	..

0 = absent; − = no record made.

ventricular pressure and the presence of the P pulmonale but as only three of the cases show this feature little can be deduced. Wood (1948) also failed to show any strict proportional relationship between intracardiac pressures and the P pulmonale. Similarly, no strict relationship exists between the degree of strain and the mean ventricular pressure, in fact it is quite striking that the most extensive appearances of strain seem to be associated with pressures little above normal. Conduction delay and incomplete right branch bundle block are similarly associated with pressures in all ranges.

Barber *et al.* (1950) in their cases of congenital atrial septal defect noted the lack of elevation of the pulmonary arterial and right ventricular pressure, yet right branch bundle block, complete or incomplete, was present in almost all of the cases. The evidence, however, was not sufficient for them to suggest whether this conduction defect was congenital or was associated more with hypertrophy or dilatation of the right ventricle, but they point out that dilatation may produce homolateral branch bundle block experimentally or in pulmonary embolism, and that dilatation is a frequent and early accompaniment of congenital atrial septal defect.

The diagnostic significance of the signs of conduction delay and incomplete right branch bundle

block are discussed by Wilson *et al.* (1947) and by Myers *et al.* (1948). The latter considered that conduction delay of 0·03 to 0·05 sec. in the intrinsic deflection after the start of the QRS in the right-sided chest leads was part of the cardiographic picture of right ventricular hypertrophy while incomplete right branch bundle block might be associated with dilatation of the right ventricle or other temporary phenomena. The distinction between these two forms of delayed conduction is not always clear. In one case of incomplete right branch bundle block in the present series there was no notching of R yet the intrinsic deflection was delayed to 0·06 sec. after the start of QRS (in V1, Fig. 2). None of the cases showing right-sided conduction delay or incomplete right branch bundle block developed any change in the pattern when observed over many months. It seems possible that incomplete right branch bundle block in cases of chronic cor pulmonale is often a further stage of the conduction delay associated with hypertrophy, while the pattern of right ventricular strain has a rather different origin associated perhaps with dilatation of the right ventricle.

Summary and Conclusions

An analysis of the electrocardiographic data of 20 cases of well established clinical cor pulmonale with congestive heart failure is presented and shows that multiple unipolar lead electrocardiography is most useful in confirming the diagnosis.

The presence of the P pulmonale, a tall peaked P wave 2·5 mm. or more in height in the limb leads or 3·0 mm. or more in the chest leads, is a most useful sign that does not appear to be related to the position of the heart in the thorax. This sign disappeared as the clinical state improved in two cases without any change in the cardiographic position of the heart.

The derivation and significance of the R wave in lead aVR is studied using multiple unipolar chest and limb leads. It is concluded that the late R wave in aVR and in V3R is often related to right ventricular excitation in chronic cor pulmonale. Right ventricular hypertrophy may be suspected when leads aVR and V3R show a late R wave even in the presence of a vertical heart with clockwise rotation, but only when complete right branch bundle block is absent.

Conduction delay in V3R, V1, or V2 when absent in V5 and V6 is useful confirmatory evidence of right ventricular hypertrophy. Conduction delay is defined as delay of the intrinsic deflection to between 0·03 and 0·05 sec. after the start of the QRS when QRS measures 0·12 sec. or less.

Incomplete right branch bundle block, defined as delay of the intrinsic deflection in V3R, V1, or V2 to between 0·05 and 0·075 sec. after the start of a QRS wave which is not over 0·12 sec. in duration, and where the intrinsic deflection in V5 and V6 is not delayed, is discussed and is suggested also to be associated with right ventricular hypertrophy.

Right ventricular strain, defined as the appearance of inversion of the T wave in all the right-sided chest leads across to V2, V3, or V4 is not necessarily due to right ventricular hypertrophy, but is often associated with acute phases in the course of chronic cor pulmonale and may disappear as the clinical condition improves. It is suggested that this pattern may accompany right ventricular dilatation.

Intracardiac pressures recorded after cardiac catheterization in 12 cases of chronic cor pulmonale are presented. There was no direct relationship between the degree of cardiographic right ventricular strain and the level of mean right ventricular pressure. Similarly, right-sided conduction delay and incomplete right branch bundle block were not directly related to the degree of elevation of right ventricular pressure.

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References

Barber, J. M., Magidson, O., and Wood, P. (1950). *Brit. Heart J.*, **12**, 277.
Barnes, A. R., and Whitten, M. B. (1929). *Ibid.*, **5**, 14.
Cohn, A. E., and Raisbeck, M. J. (1921–2). *Heart*, **9**, 311.
Einthoven, W. (1906). *Arch. Internat. Physiol.*, **4**, 132.
Goldberger, E. (1949). *Unipolar Lead Electrocardiography*. 2nd ed., London, Henry Kimpton.
Hecht, H. A. (1946). *Amer. Heart J.*, **32**, 39.
Hermann, G. R., and Wilson, F. N. (1921–2). *Heart*, **9**, 91.
Katz, L. N. (1946). *Electrocardiography*. 2nd ed., London, Henry Kimpton.
——, and Weinstein, W. (1947). *Med. Clin. N. Amer.*, **31**, 172.
Lewis, T. (1925). *The Mechanism and Graphic Registration of the Heart Beat*, p. 135 *et seq.*, 3rd ed., London, Shaw & Sons, Ltd.
Myers, G. B., Klein, H. A., Stoffer, B. E. (1948). *Amer. Heart J.*, **35**, 1.
Schlesinger, P.; Beuchimol, A. B., and Cotrim, M. R. (1949). *Ibid.*, **37**, 1110.
Sodi-Pallares, D., Vizcaino, M., Soberon, J., and Cabrera, E. (1947). *Ibid.*, **33**, 819.
White, P. D., Smithwick, P. H., Mathews, M. W., and Evans, E. (1945). *Ibid.*, **30**, 165.
Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmahn, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S. (1944). *Ibid.*, **27**, 19.
——, Rosenbaum, F. F., and Johnston, F. D. (1947). *Advances in Internal Medicine*, Vol. II, p. 39. New York, Inter-science Publishers, Inc.
Wood, P. (1948). *Brit. Heart J.*, **10**, 87.
——, and Selzer, A. (1939). *Ibid.*, **1**, 49.
Zuckermann, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D. (1948). *Amer. Heart J.*, **35**, 421.

CARDIAC INFARCTION WITH PAIN CONFINED TO EFFORT

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Occlusion of a coronary artery has long been regarded as a possible basis for angina of effort, but it was not realized that it might be the usual cause until the pathological work of Blumgart, *et al.* (1940). In angina of effort (without cardiac hypertrophy, aortic syphilis, or anæmia) they demonstrated by post-mortem injection studies the invariable presence of occlusion of at least two main branches of the coronary arteries. In some of these cases myocardial infarction had followed the occlusion without the clinical counterpart of prolonged rest pain: this conforms with clinical experience for it is not uncommon to find electrocardiographic evidence of myocardial infarction when cardiac pain is confined to effort. So far as we know, the first reported case of this type is that of Bourne (1939). The object of this paper is to determine how often this is so and to compare our clinical observations with the electrocardiographic evidence.

METHODS

Selection of cases. Between January, 1946 and April, 1949, 291 patients were seen who complained of pain considered to be of cardiac origin, and in 97 cases the pain was apparently confined to effort. At the time of this investigation, 82 of these patients were available, 8 having died without the opportunity for necropsy and 7 being untraced. These 82 patients were personally re-interviewed and 20 were rejected on the grounds given below:—

Pain on effort but lasting on occasions more than 15 minutes	9 cases
Pain of short duration but sometimes occurring at rest	7 cases
Pain so atypical as to be of uncertain origin	3 cases
Positive Wassermann reaction	1 case

The 62 selected patients complied with the following criteria.

(1) They complained of pain described as constricting, choking, pressing, aching, or burning, either retrosternal or radiating from some part of the chest to one or both arms or to the neck or jaw.

(2) The pain was constantly related to effort, had never occurred at rest, and was invariably rapidly relieved by rest, never persisting for more than 15 minutes.

(3) There was no clinical or radiological evidence of a valvular lesion. (With the exception of one case in which the combination of a basal systolic murmur, slight left ventricular enlargement and a normal blood pressure made it impossible to exclude aortic valve disease).

(4) The blood count was normal and the Wassermann reaction negative.

(3) and (4) were introduced to exclude certain cases in which there might be some other cause for relative myocardial ischæmia.

In selecting these cases re-interviewing was found to be essential, for an initial prolonged attack of cardiac pain was not always mentioned at the first interview, as illustrated by the following cases.

A man of 45 first attended the clinic in October, 1947, complaining of a mid-sternal crushing pain occurring when walking rapidly and immediately relieved by rest, which had been present for six weeks. He denied having any prolonged attack of pain. On re-interview he admitted that the initial attack, which had occurred when hurrying with a heavy bag, had lasted half an hour and had been so severe that he voluntarily spent three days in bed. Effort pain had been present since resuming activity. The electrocardiogram showed changes diagnostic of posterior myocardial infarction.

A man of 50 attended the clinic in August, 1948, complaining solely of retrosternal burning pain on effort relieved by rest. On re-interview he recollected being awakened one night in June, 1948, by severe epigastric pain lasting some hours and associated with vomiting. The following day he first noticed the effort pain. He regarded the initial attack as gastric in origin and therefore of no importance. The electrocardiogram showed changes diagnostic of posterior myocardial infarction.

Electrocardiographic Technique. A routine cardiogram had already been taken on the occasion of the patient's initial visit to the clinic. Unless this showed unequivocal evidence of infarction, we made what we considered to be an adequate electrocardiographic investigation. In all cases this included the standard limb leads, the unipolar limb leads, 6 præcordial leads in the positions 1 to 6, and 6 high præcordial leads taken one* interspace above the corresponding normal position.

In recording the præcordial leads the exploring electrode was paired with the central terminal of Wilson (1943) using 5000 ohm resistances. The unipolar limb leads were recorded by Goldberger's (1942) technique but 5000 ohm resistances were inserted in the limb connections to the indifferent electrode as recommended by Wilson (1943) and Bryant, Johnston, and Wilson (1949).

Criteria for Diagnosis of Infarction. Principles governing the electrocardiographic diagnosis of infarction have been laid down by Wilson and his associates (1933, 1934, 1935). The application of these principles to the patterns occurring in the præcordial leads in association with infarction of the anterior free wall of the left ventricle and the septum has been clearly described (Wilson, 1944), and further electrocardiographic and pathological correlation has been carried out by Myers *et al.* (1948*a*, 1948*b*, 1949*a*, 1949*b*), We have followed their criteria, which may be summarized as the combination of two of the following three types of change in leads facing ventricular muscle.

(1) Characteristic QRS changes.
  (*a*) Q waves of more than 0·03 seconds duration from onset to lowest point.
  (*b*) Absent R waves from complexes normally of RS type.
(2) Elevation of S–T segment by more than 0·4 mV.
(3) T wave changes of a form and distribution not explicable by ventricular enlargement.

The changes in form of the ventricular complex to be accepted as diagnostic of infarction of the posterior free wall of the left ventricle are, however, much less certain, for the form of the complex in the foot lead is profoundly affected by changes in the electrical position of the heart. Myers and Oran (1945) studying the form of lead VF in 25 cases of posterior infarction proven by autopsy or œsophageal leads, concluded that, although a Q of more than 25 per cent of the amplitude of the succeeding R was suggestive of infarction and absence of a Q wave was strongly against infarction, diagnostic evidence was difficult to obtain. In more recent articles Myers *et el.* (1949*c*, 1949*d*) have studied the form of lead VF in different electrical positions of the heart and have shown that posterior infarction is often not recognizable in VF when the heart is electrically horizontal or semi-horizontal. On the basis of their work, we have regarded the foot lead as diagnostic only when both the following changes were present—(1) A Q wave of at least 0·03 seconds duration from onset to lowest point followed by a small R and deep S or a tall late R: or a QS deflection in an electrically intermediate to vertical heart (left bundle branch block must be excluded for this may give rise to a broad slurred QS or QR complex), and (2) Characteristic changes in the ST-T complex.

Two examples of posterior infarction, from the present series of cases, are shown in Fig. 1. The upper record shows the standard and unipolar limb leads from a man of 51 who had suffered anginal pain on effort for five years. The Q wave in lead VF is of almost 0·04 sec. duration from onset to lowest point and the corresponding T wave is deeply and symmetrically inverted. The

*We now usually take high præcordial leads two spaces above the usual positions.

electrical position is intermediate. The lower record shows the standard limb, unipolar limb and præcordial leads from a man of 50 who had had angina of effort for almost three years. Here the Q wave in VF is 0·03 sec. in duration and the T wave inversion is less striking than in the upper record. Since the electrical position of the heart is semi-vertical, we regard these changes as diagnostic of posterior infarction but they are the minimum changes that we would accept.

Classification of Electrocardiograms. If two of the three types of change in the ventricular complex already enumerated were present we classed the electrocardiogram as diagnostic of infarction. If only one type of change was present we classed it as abnormal, and suggestive but not

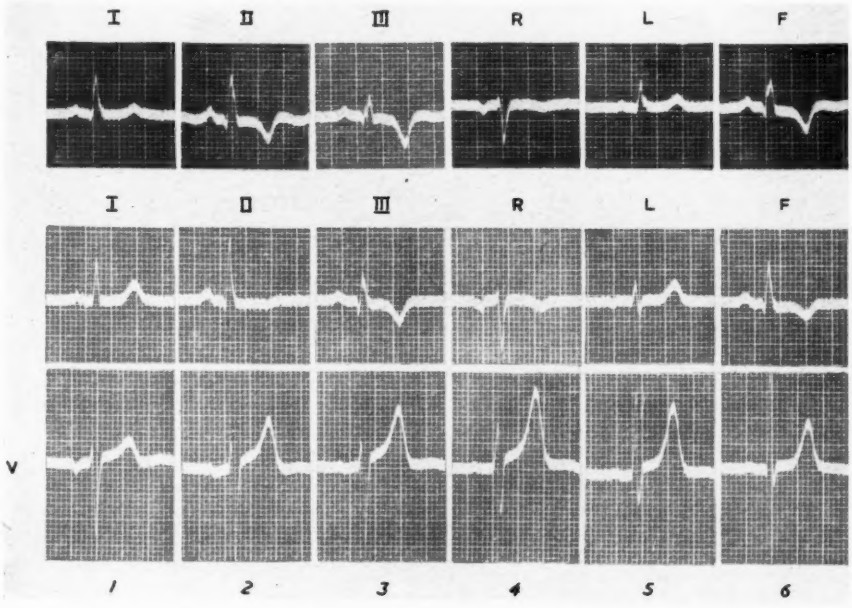

FIG. 1.—Electrocardiograms from two patients showing changes regarded as diagnostic of posterior infarction. The lower record shows the minimum changes accepted as diagnostic.

diagnostic of infarction. Two typical cardiograms from this group are shown in Fig. 2 and 3. Fig. 2, from a 65-year-old woman who had suffered from classic effort angina for eight years shows symmetrical T wave inversion from the second to the sixth position in both the normal and high præcordial leads. The QRS complexes are within normal limits and there is no S–T displacement. Fig. 3 is from a 54-year-old woman who had suffered from angina of effort for only five weeks. Here the T wave abnormalities are localized to V2, V3, and V4 and the corresponding high leads. The QRS complexes are within normal limits. In neither case do we think the T wave changes are explicable by ventricular enlargement. The remaining records were classified as showing other abnormalities or as being within normal limits.

RESULTS

The selected group comprised 53 men and 9 women whose ages ranged from 31 to 74 years. Forty-eight had normal blood pressure and 14 had a persistent diastolic pressure of 105 mm. of Hg. or greater. Six of the group with normal blood pressure showed radiological evidence of enlarge-

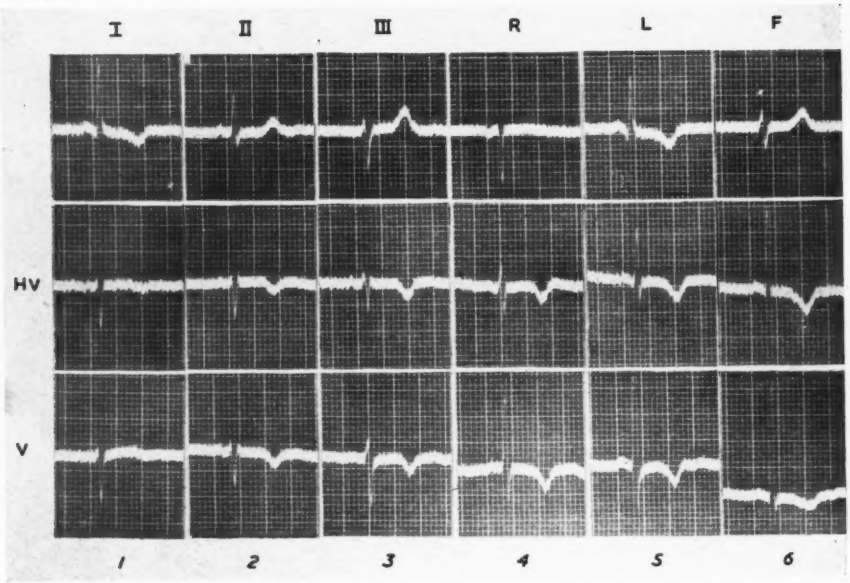

FIG. 2.—Example of an electrocardiogram regarded as abnormal and suggestive of infarction. There are widespread T wave changes extending from V2 to V6 which are not entirely explicable by ventricular enlargement.

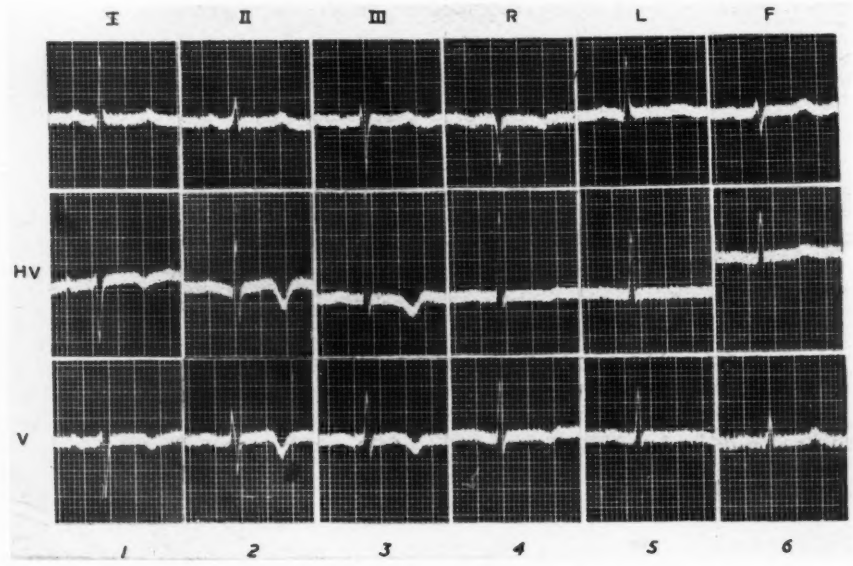

FIG. 3.—T wave changes confined to V2, V3 and V4 and the corresponding high leads. This record was regarded as abnormal and suggestive of infarction.

ment of the left ventricle suggesting the possibility of past hypertension. The electrocardiographic evidence is given below.

Electrocardiograms diagnostic of infarction	17 cases
Electrocardiograms abnormal and suggestive of infarction	14 cases
Electrocardiograms within normal limits	23 cases
Electrocardiograms showing other abnormalities	8 cases

Twelve infarctions were situated posteriorly and therefore diagnosed from the limb leads. There were five anterior infarcts and in two of them the limb leads were within normal limits.

Site of Infarct.	No.	Limb leads diagnostic	Limb leads abnormal	Limb leads normal
Posterior ..	12	12	0	0
Anterior ..	5	0	3	2

Fig. 4 shows two records from one of these two cases, a man of 57. When the first electrocardiogram (A) was taken angina of effort had been present for only six weeks. V2 and V4 show diagnostic changes with absent initial R waves, S–T elevation, and terminal inversion of the T waves. The standard limb leads are within normal limits though TI is of low voltage. Two months later (B) TI has become negative because the T wave changes have spread far enough to the left to modify the left arm lead. Changes confined to the centre of the præcordium will rarely be transmitted to the limb leads.

In 14 cases the electrocardiograms were abnormal and suggestive of infarction. The abnormalities were confined to negative T waves in the præcordial leads not explicable by ventricular enlargement in 11 cases; in the remaining 3 they were confined to the QRS complexes.

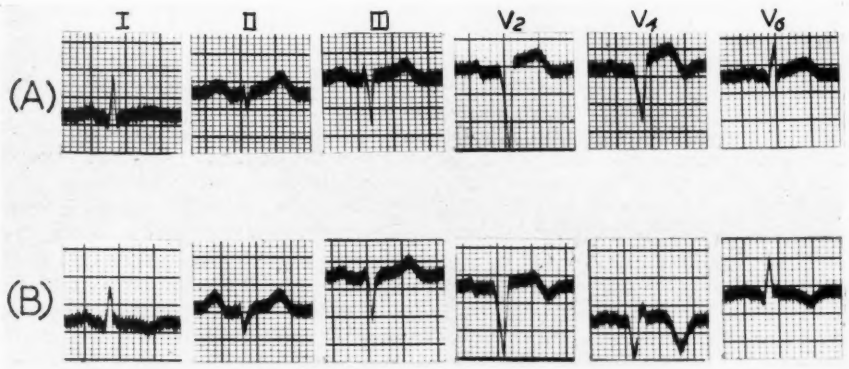

Fig. 4.—Two electrocardiograms from the same case. (A) six weeks after the onset of angina of effort, shows normal limb leads but changes diagnostic of infarction in V2 and V4. (B) three months later, shows that T wave changes have extended to V6 and therefore appear in lead I.

The proportion of definite infarcts was lower in the cases with hypertension or radiological evidence of cardiac enlargement than in those with a normal blood pressure and without radiological cardiac enlargement; on the other hand, the proportion of doubtful infarcts was higher in the group with cardiac enlargement.

	No.	Definite infarcts	Doubtful infarcts	No infarcts
Cases without cardiac enlargement ..	42	15	7	20
Cases with enlarged hearts	20	2	7	11

It may be that when the heart is enlarged, angina of effort occurs more readily in the absence of

infarction, but the number of cases is not sufficient to justify any firm conclusion on this point. The high præcordial leads were recorded in 44 cases but we did not derive any additional information from them.

Discussion

We believe that our diagnostic criteria were sufficiently strict to ensure that myocardial infarction was not diagnosed unless it had certainly occurred. On the other hand there are reasons why the clinical data should underestimate the incidence of infarction. In the first place, infarction may occur in a site inaccessible to ordinary electrocardiographic examination and this is often so when the posterior free wall of the left ventricle is involved. Myers *et al.* (1949*c*, 1949*d*) found changes diagnostic of posterior infarction in only 11 of 35 cases in which the heart was electrically horizontal, despite extensive old posterior infarction at necropsy. When the heart was electrically intermediate to vertical the proportion of healed infarctions diagnosed cardiographically increased to 42 out of 75. Secondly, diagnostic changes in the cardiogram may disappear in time; changes in the ST–T complex are usually transient and even changes in the QRS complex may not be permanent. Wilson (1943) has reported a case in which R waves, absent shortly after clinical coronary occlusion, returned later and a similar case (not included in the present series) is illustrated in Fig. 5. The patient, a man of 51, had a clinical coronary occlusion on October 29. The electrocardiogram taken on October 30 (Fig. 5A) showed absent R waves in V2 and V3, a Q wave of abnormal duration (0·03 sec.) in V4 and inversion of the T waves in V4 and V5. Three months later (Fig. 5B) the record was within normal limits.

There are likely to be even more cases with coronary occlusion than the number of cardiac infarctions suggests, for Blumgart *et al.* (1941*a* and *b*) have shown that coronary occlusion may not be followed by cardiac infarction and possibly not even by permanent ischæmia of sufficient extent to affect the electrocardiogram.

Making allowance for the inadequacy of the electrocardiogram as a means of detecting healed infarction, and for the fact that coronary occlusion may occur without consequent myocardial infarction, it seems to us that our results are not inconsistent with the conclusion of Blumgart *et al.* (1940) that in the absence of cardiac enlargement, syphilis, or anæmia, occlusion of a major coronary vessel is the usual underlying cause of the ischæmia associated with angina of effort. If we accept this conclusion, it leads us to regard angina of sudden onset as evidence of coronary occlusion (with or without infarction). If the onset of the angina is recent, then the management of the case will be similar to that usually adopted in recent cardiac infarction, though possibly rest in bed need not be so prolonged. Bourne (1939) reported a case in which the cardiogram taken 4 weeks after the sudden onset of angina of effort showed a negative T wave in lead IV which had reverted to normal 8 weeks later; he attributed the negative TIV to coronary thrombosis and concluded that a patient may present symptoms of angina of effort as a result of coronary thrombosis. With this conclusion we entirely agree. However, since coronary occlusion need not be followed by cardiac infarction, or even by myocardial ischæmia sufficient to produce T wave changes on the cardiogram, we regard angina of sudden onset as evidence of coronary occlusion *whether the electrocardiogram is normal or not*. The wisdom of adopting this attitude in practice is illustrated by the following case.

A man of 45 consulted one of us (A.M.J.) because 2 weeks previously he had suddenly developed severe constricting pain in the chest whenever he walked 20 to 30 yards. This was rapidly relieved by rest or trinitrin and was in every way typical of severe angina of effort. In these circumstances cardiographic evidence of recent cardiac infarction might be expected, but in this case the cardiogram was entirely normal (Fig. 6). Nevertheless, it was assumed that a coronary occlusion had occurred two weeks previously and rest in bed was advised. Ten days later the patient insisted on getting up, however, and went into the garden where he collapsed and died within a few minutes.

It seems possible that had this man rested for a sufficient period to permit the establishment of a collateral circulation, death would not have occurred so soon.

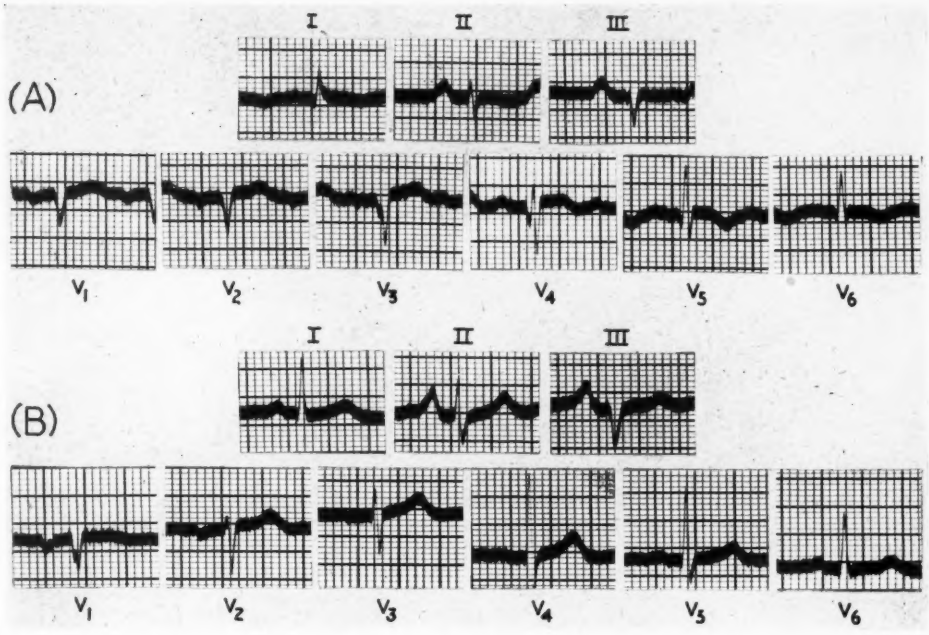

FIG. 5.—Two electrocardiograms from the same case. (A) Diagnostic changes of infarction in V3 to V6 on the day after the infarction. (B) Three months later, is entirely normal, with recovery of the R waves, in addition to the disappearance of T wave changes.

SUMMARY

Ninety-seven consecutive cases of angina of effort have been reviewed: 82 were available for re-interview; in 62 of these typical angina of effort was present and pain had never occurred at rest or persisted longer than 15 minutes.

If the routine cardiogram did not reveal diagnostic evidence of infarction an additional cardiogram was taken comprising standard and unipolar limb leads, 6 unipolar præcordial leads in the positions 1–6 and 6 high unipolar præcordial leads.

Diagnostic evidence of myocardial infarction was present in 17 cases, and in a further 14 cases the records were abnormal and suggestive of infarction or ischæmia.

The pathological evidence concerning the relationship between coronary occlusion and myocardial infarction is briefly discussed and related to the clinical data presented. Our clinical observations are not inconsistent with the view that in the absence of other causes of relative myocardial ischæmia such as cardiac hypertrophy, angina of effort is usually due to coronary occlusion with or without subsequent myocardial infarction. It is suggested that the sudden appearance of angina of effort, or the sudden exacerbation of symptoms in established angina, should be regarded as an indication of coronary occlusion at that time whether the electrocardiogram shows evidence of infarction or not.

We wish to thank Professor Crighton Bramwell, in whose department these observations were made, for his advice and help, and Mr. T. Corless for his technical help in the preparation of the electrocardiograms.

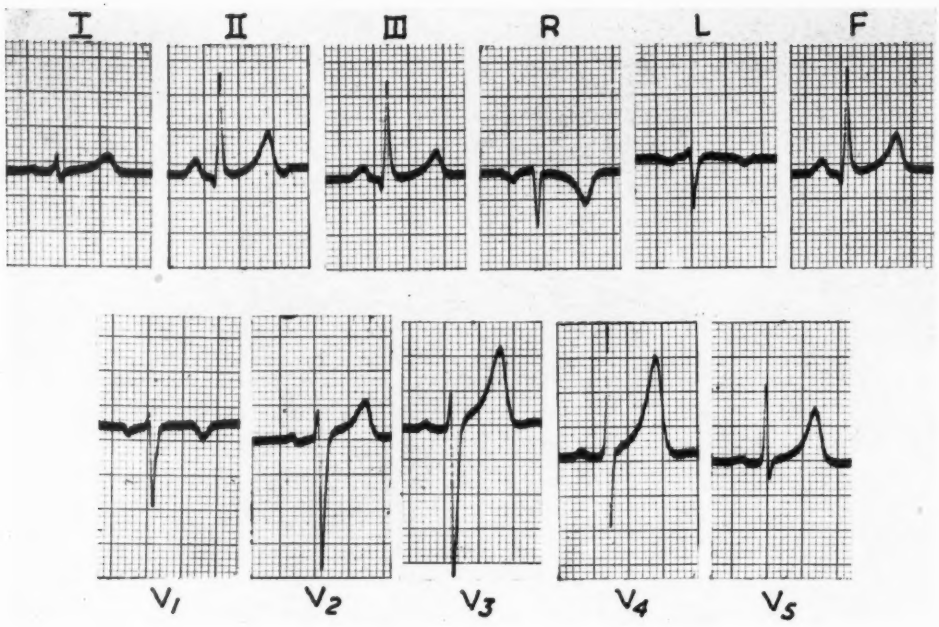

FIG. 6.—Normal electrocardiogram from a case of recent angina of effort in which death occurred 10 days later.

REFERENCES

Blumgart, H. L., Schlesinger, M. J., and Davis, D. (1940). *Amer. Heart J.*, **19**, 1.
——, Gilligan, D. R., and Schlesinger, M. J. (1941*a*). *Ibid.*, **22**, 374.
——, ——, and Zoll, P. M. (1941*b*). *J. Amer. med. Assoc.*, **116**, 91.
Bourne, G. (1939). *Lancet*, **1**, 1155.
Bryant, J. M., Johnston, F. D., and Wilson, F. N. (1949). *Amer. Heart J.*, **37**, 321.
Goldberger, E. (1942). *Ibid.*, **23**, 483.
—— (1947). *Unipolar Lead Electrocardiography*. London : H. Kimpton.
Myers, C. B., and Oran, B. G. (1945). *Amer. Heart J.*, **29**, 708.
——, Klein, H. A., and Stofer, B. E. (1948*a*). *Ibid.*, **36**, 535.
——, ——, and Hiratzka, T. (1948*b*). *Ibid.*, **36**, 838.
——, ——, —— (1949*a*). *Ibid.*, **37**, 205.
——, ——, —— (1949*b*). *Ibid.*, **37**, 720.
——, ——, —— (1949*c*). *Ibid.*, **38**, 547.
——, ——, —— (1949*d*). *Ibid.*, **38**, 837.
Wilson, F. N. (1943). *Trans. Assoc Life Insur. M. Dir. America* (1942), **29**, 154,
——, Johnston, F. D., Macleod, A. G., and Barker, P. S. (1934). *Amer. Heart J.*, **9**, 447.
——, Hill, I. G. W., and Johnston, F. D. (1935). *Ibid.*, **10**, 163.
——, ——, Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S. (1944). *Ibid.*, **27**, 19.
——, Macloed, A. G., and Barker, P. S. (1933). *Heart*, **16**, 155.

THE CLINICAL SIGNIFICANCE OF GALLOP RHYTHM IN HYPERTENSION

BY

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Gallop rhythm is widely held to be a sign of prognostic value, and this opinion has been supported by follow-up studies of patients with gallop rhythm in groups of mixed ætiology. This method of assessment is, however, open to criticism; first, because it is so dependent upon the way in which the patients are selected, and secondly, because the prognostic significance of gallop rhythm is clearly not the same in different diseases. This paper reports a clinical and phonocardiographic study of 100 hypertensive subjects, 37 of whom had gallop rhythm. The presence or absence of the various types of gallop has been correlated with the blood pressure, heart size, degree of cardiac failure, and electrocardiogram.

Definition and Nomenclature

Gallop rhythm is here defined as the presence, in a patient with heart disease, of audible vibrations in diastole, homologous either with the physiological third or auricular sounds. A phonocardiographic classification is used. The gallop sound coincident with the third sound which occurs during rapid ventricular filling, is called " rapid filling " gallop. That corresponding with the auricular sound and dependent upon auricular systole is called " auricular " gallop. A gallop occurring when diastole is so shortened by tachycardia that the rapid ventricular filling phase merges with auricular systole is called " indeterminate " gallop.

The use of the terms " rapid filling " and " auricular " gallop follows the classification used by Lian, Minot, and Welti (1941) and Frost (1949). They seem preferable to " protodiastolic " and " presystolic " gallop, since the former never occurs in protodiastole, and may even occur in the second half of diastole, whereas the latter is at times mid-diastolic. A second alternative, namely, subdivisions of the third sound and fourth sound (Evans, 1943), has the disadvantage that these may be confused with their physiological counterparts; it is also perplexing to call the earliest sound in the cardiac cycle the fourth. At all events, each of these three classifications should be confined to phonocardiographic diagnosis. Clinically, it is best to describe early, mid-, and late diastolic gallops. The term indeterminate gallop has been coined as no other suitable name exists. The summation gallop of Wolferth and Margolies (1931) originally referred to the gallop that may arise when subaudible protodiastolic and presystolic vibrations merge during tachycardia, and by summation become audible. It remains a valuable term when restricted to this connotation. The epithet " gallop " has been retained; it has survived its centenary.

Clinical Material

One hundred patients with hypertension were studied: 62 women and 38 men. All had average " casual " diastolic pressures above 95. Their average age was 57 years (range 18–80). The ætiological groups were as follows: essential hypertension 91, chronic nephritis 3, chronic pyelonephritis 2, toxæmia of pregnancy 3, and coarctation of the aorta 1.

Thirteen had angina pectoris and 35 were considered obese. Cases with valvular disease, anæmia, thyrotoxicosis, substantial lung disease, or recent myocardial infarction were excluded. The patients derived from two sources; the cardiovascular clinic (47), and the medical wards (53) of the Dunedin Public Hospital, New Zealand. All available cases from the cardiovascular clinic were studied, and most of the cases from the wards. Patients with marked dyspnœa at rest were usually excluded for technical reasons. Otherwise they were unselected. The majority were moderately severe or severe cases.

Methods

Clinical interpretation of heart sounds. The patients, unless orthopnœic, lay supine on a couch. The heart was examined with a stethoscope at the apex and near the xiphisternum. A clinical diagnosis of any abnormal sound was recorded with the qualifications definite, probable, or possible, and the loudness and site of maximum audibility were noted. No special manœuvres were employed to try to bring out a gallop sound. The results of previous auscultation were ignored.

Apparatus and recording procedure. The apparatus used was a six-channel oscilloscope designed and constructed in the Department of Medicine of Otago University. The input was derived from a Maico Stethetron pick-up head and tracings were recorded on 35-mm. film. The frequency response curves corresponded closely with the linear, stethoscopic, and logarithmic curves recommended by Rappaport and Sprague (1942). Additional information about the instrument and its acoustic properties have been published elsewhere (Miles, 1950).

As a reference trace for timing phonocardiographic events, a standard lead II electrocardiogram was used: this was considered adequate in the present group of patients where the main difficulty was in distinguishing auricular gallops from split first sounds. Whilst recording the tracings, first at the apex and then in the xiphisternal region, the various channels were checked visually on the monitor oscilloscope, and at the same time the heart sounds were heard with the monitor stethoscope fed from the same pick-up head. About 18 inches of film were used for each patient.

Phonocardiographic interpretation of heart sounds. Audible vibrations beginning between 0·11 and 0·20 sec. after the onset of the second sound were considered to be rapid filling gallops. Those occurring between the apex of the P wave and the apex of the R wave in the reference electrocardiogram were considered to be auricular gallops. It is realized that these standards are arbitrary, and that some of the indeterminate gallops would have been classified as auricular gallops by other authors (Orías and Braun-Menéndez, 1939; Lian *et al.*, 1941). These diagnoses were made from the logarithmic traces except in the few cases in which the logarithmic channel was not recording properly. Even so, it was not always possible to be certain what had actually been heard. A phonocardiograph can at best only show what is potentially audible. This difficulty sometimes arose when a small auricular vibration and also a split first sound were recorded in the same patient. Three specimen phonocardiograms are shown in Fig. 1.

Final diagnosis of heart sounds. Before gallop rhythm was finally accepted, it had to be both heard and recorded. The few heard but not recorded and vice versa were excluded.

Grading of Associated Findings

Blood pressure. It was decided to use the more significant diastolic pressure rather than the more easily determined systolic. The average of several "casual" diastolic pressures was taken, the casual pressure being the lowest recorded after about five minutes with the patient at rest in the outpatient department or ward. In 64 patients a basal blood pressure was also taken, by the method recommended by the committee of the British Cardiac Society and the American Heart Association.

The patient was first graded according to his casual diastolic pressure as follows: Grade I, 96–105; Grade II, 106–115; Grade III, 116–125; Grade IV, more than 125. If the basal

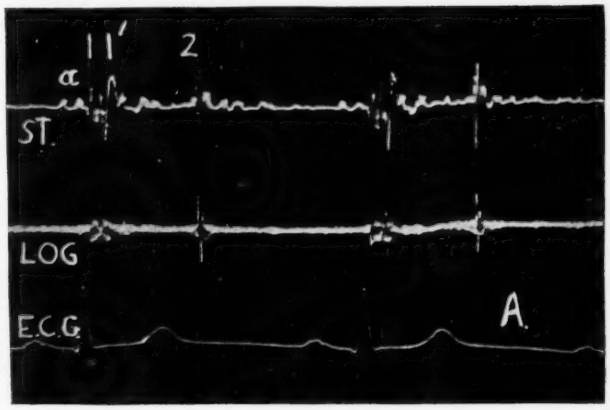
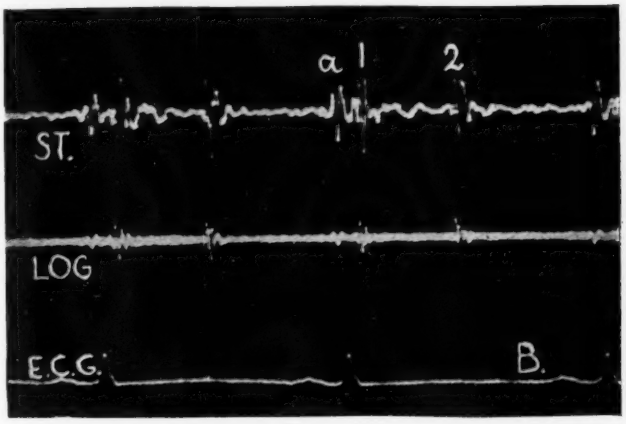
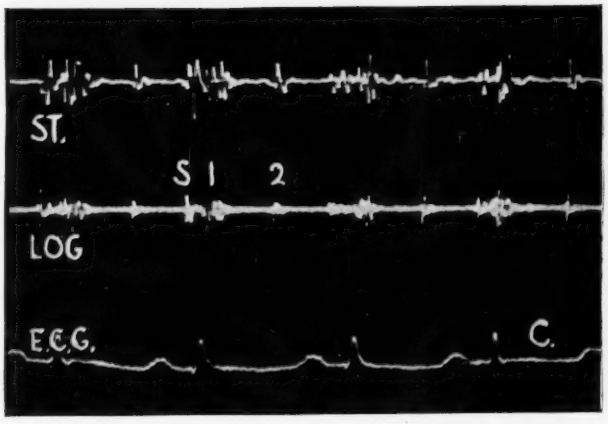


FIG. 1.—Three specimen phonocardiograms. St = stethoscopic trace. Log. = logarithmic trace. 1 = 1st sound. 2 = 2nd sound. 11′ = split 1st sound. a = auricular vibrations. S = indeterminate gallop. Scale: 1 cm. = 0·2 sec.

(A) *Split 1st sound.* Auricular vibrations (preceding the apex of the electrocardiogram R wave) are present in the stethoscopic but not in the logarithmic trace.



(B) *Auricular gallop.* Auricular vibrations are present in both stethoscopic and logarithmic traces.



(C) *Indeterminate gallop.* Owing to tachycardia (rate 130) the gallop sound (S) satisfies the criteria for both rapid filling gallop (< 0·2 sec. after onset, 2nd sound) and auricular gallop (between apex of P wave and apex of R wave in electrocardiogram reference trace).

diastolic pressure was more than 20 mm. below the lowest figure of the previously assigned casual diastolic pressure grade, this grade was lowered by 1, provided that the casual pressure was not above 135 mm. Hg. Nine were lowered in this way. One patient, with a casual pressure of 210/128 and a basal pressure of 128/80 was lowered from Grade IV to Grade II.

Heart size. The size of the heart was judged by eye from a postero-anterior teleradiogram. Thirteen cases were screened as well. The grades (I–IV) were normal limits, slight enlargement, moderate enlargement, and gross enlargement.

Degree of cardiac failure. The following four grades were recognized: no dyspnœa on level walking; dyspnœa on level walking; dyspnœa at rest (orthopnœa and paroxysmal dyspnœa) and right-sided cardiac failure (with raised venous pressure). Breathlessness on hills only, may often have been due to early left ventricular failure, but the significance of minor degrees of this symptom is difficult to assess.

Electrocardiographic changes. An abnormal group was recognized, comprising cases with left ventricular strain, old myocardial infarction, bundle branch block, and atypical tracings, and a normal which included simple left axis deviation.

Results

The final clinical and phonocardiographic diagnoses of the heart sounds are shown below.

Dual rhythm	44	No gallop group 63.
Split 1st sound	17	
Systolic triple rhythm	2	
Auricular gallop	23	Gallop group 37.
Rapid filling gallop	6	
Indeterminate gallop	8	

Of 41 cases believed on clinical grounds to have gallop rhythm 8 had no good phonocardiographic evidence of it; most of them having split first sounds. Of 23 cases judged clinically to have splitting of the first sound 4 were shown to have auricular gallop. The clinical findings are shown below.

	Blood pressure	Heart size	Degree of failure
Grade I	16	28	46
Grade II	25	25	35
Grade III	26	22	11
Grade IV	33	25	8

The electrocardiographic findings were abnormal in 52 cases: left ventricular strain in 34, old myocardial infarct in 3, atypical in 8, and bundle branch block in 7 cases. They were normal in the remaining 48, though 30 showed some left axis deviation. The P–R interval was less than 0·16 sec. in 23; between 0·16 and 0·20 in 63; and greater than 0·20 sec. in 7: the remaining 7 had auricular fibrillation.

Fig. 2 shows the number of cases with and without gallop rhythm in each grade of blood pressure, heart size, and degree of cardiac failure; and in those with normal and abnormal electrocardiograms. A distinct tendency is shown for the more advanced cases to be associated with gallop rhythm, which was present in more than half the patients in the fourth grades. The three different gallop groups are analysed below.

Auricular gallop group. This comprised 23 cases, 10 men and 13 women of average age 51 years (range 23–71). At the time of recording, the average pulse rate was 90 (range 60–110).

Fig. 2 reveals a statistically significant correlation between auricular gallop and Grade IV hypertension and also between auricular gallop and an abnormal electrocardiogram. There is no such striking correlation with Grade IV heart size or Grade IV cardiac failure. None of the cases with the lowest grade of hypertension had auricular gallop. It is of interest that 6 (26%) of the auricular

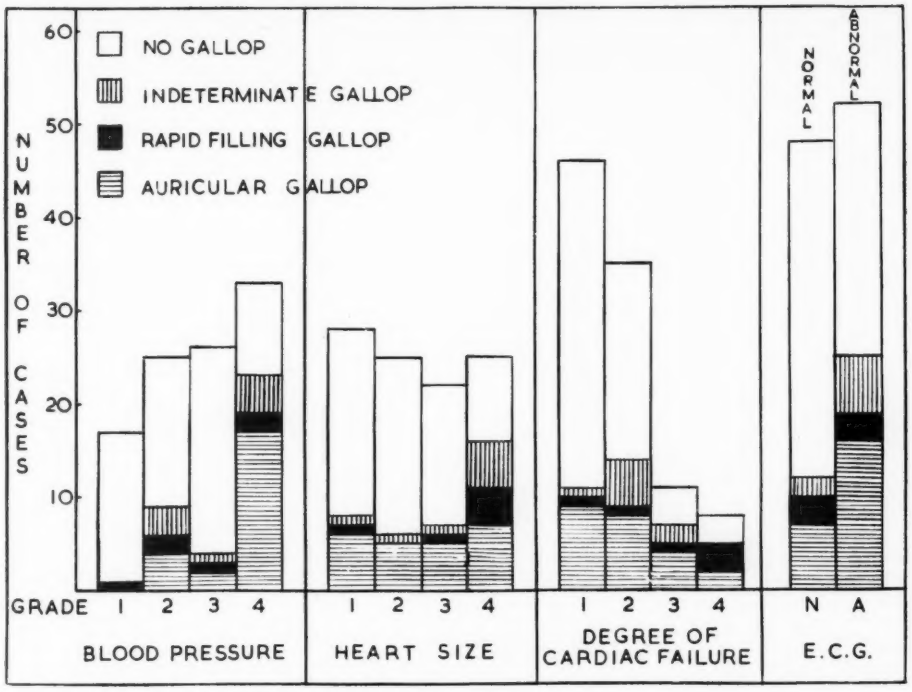


FIG. 2.—Number of cases with and without gallop rhythm in each grade (see text).

gallop cases had apparently normal sized hearts, 9 (39%) had no breathlessness on walking on the flat, and 7 (30%) had electrocardiograms within normal limits. Three of the cases had neither enlargement of the heart nor shortness of breath on the flat. One patient, aged 23, with Grade IV hypertension and a loud auricular gallop, was able to enjoy a full day's shooting expedition.

No correlation was observed between the loudness of the auricular gallop and the severity of the case. Nor was any relation noticed between the severity of the case and the interval between the gallop and first sound. Five of the auricular gallop cases had P–R intervals exceeding 0·2 sec.; they were in other respects typical of the group.

Rapid filling gallop group. This comprised 6 cases; 2 men and 4 women of average age 63 years (range 52–71). Their average pulse rate at the time of recording was 93 (range 75–106). This group was unfortunately too small to allow firm conclusions to be drawn from it, but 4 of the 6 cases had gross enlargement of the heart, and 3 of them had right-sided cardiac failure, which is a statistically significant correlation, as there were only 8 cases of right-sided failure in the whole series ($\chi^2 = 15{\cdot}3$). One case, on the other hand, had neither cardiac enlargement, breathlessness when walking on the level, nor electrocardiographic change.

Two of the three gallops heard best in the xiphisternal region were rapid filling gallops. Both were associated with right-sided cardiac failure.

Indeterminate gallop group. This comprised 8 cases; 5 men and 3 women, of average age 51 years (range 31–60). At the time of recording the average pulse rate was 113 (range 100–125). Reference to Fig. 2 shows that 5 of the 8 cases had gross enlargement of the heart; 1, however, had a normal sized heart on screening and was not breathless on the flat. Six of the 8 cases had loud gallops; the gallop sometimes being the loudest of the three sounds.

The site of maximum audibility of the gallop sound is shown below.

Site best heard	Auricular gallop cases	Rapid filling gallop cases	Indeterminate gallop cases
Apex	17	2	3
Xiphisternum	0	2	1
Both equally	6	2	4

Discussion

An interesting finding was the commonness of gallop rhythm in hypertension when specially sought. The best available evidence of its absolute incidence is Garvin's (1943) finding, that 47 per cent of hypertensive patients who died a cardiac death had previously had gallop rhythm. That 37 per cent. of the present series of unselected hospital patients with hypertension, and as many as 63 per cent of those with Grade III and IV cardiac failure, had gallop rhythm when examined on a single occasion, suggests that more than 50 per cent of hypertensive subjects are likely to develop gallop rhythm sooner or later, even when taking into account that some, through obesity or emphysema, will have sounds of low intensity.

If gallop rhythm is to have prognostic value, it must either be a reliable indication that a certain stage of cardiac involvement has been reached, or a sign of a rapidly advancing disease process. The present investigation, while showing a tendency for the severer cases to be associated more often with gallop rhythm, demonstrated that in hypertension it occurs over a wide clinical range. If, then, we ignore the remote possibility that gallop rhythm is in some way correlated with the rate of progress of the hypertension, it follows that gallop rhythm is not a reliable prognostic sign.

There is surprisingly little written reference to the examples, familiar to all clinicians, of gallop rhythm occurring in patients with comparatively good cardiac function, though Duchosal (1932) does say that a certain proportion of hypertensive subjects may possess well-defined gallop rhythm for years.

This finding, that gallop rhythm may be audible under widely differing conditions, is not in the least unexpected when it is appreciated that the corresponding vibrations in the normal hearts of young people vary enormously in intensity; and, moreover, that in adults great differences occur in the transmitting properties of the lungs from emphysema and of the chest wall as a result of rigidity or obesity. It is of some interest that 43 per cent of the non-gallop cases were obese, as compared with only 22 per cent of the gallop cases, though it is true that the obese and non-obese groups were not strictly homogeneous.

Fig. 3, which compares the clinical findings in the 37 gallop cases and in the 52 with abnormal electrocardiograms, suggests that gallop rhythm has about the same overall significance as has any abnormality in the electrocardiogram. It is not doubted that gallop rhythm is a valuable clinical sign in the detection of heart disease, but it is probably a poor guide to prognosis. There are better methods for assessing the cardiac status. If two patients had the same history, blood pressure, heart size, degree of cardiac failure, and pulse rate, and one of them had gallop rhythm, there is no evidence to show that the latter would have the worse prognosis.

In addition to the claim that gallop rhythm is useful prognostically, Evans (1943), has asserted that rapid filling gallop is a sign of right- and auricular gallop of left-sided cardiac failure. In the present series, only 2 out of 23 with auricular gallop, and as many as 3 out of 6 with rapid filling gallop, had right-sided cardiac failure, thus giving some support to Evans' contention. There is also some corroboration for the view originally propounded by Potain (cited by Holt, 1927), that the gallop may be right-sided (i.e. heard best towards the xiphisternum) in cases of right-sided cardiac failure. Of the 5 cases with right-sided cardiac failure, 2 were heard best in the xiphisternum region, 1 in the apical region, and 2 equally well at both. The only other right-sided gallop was an indeter-

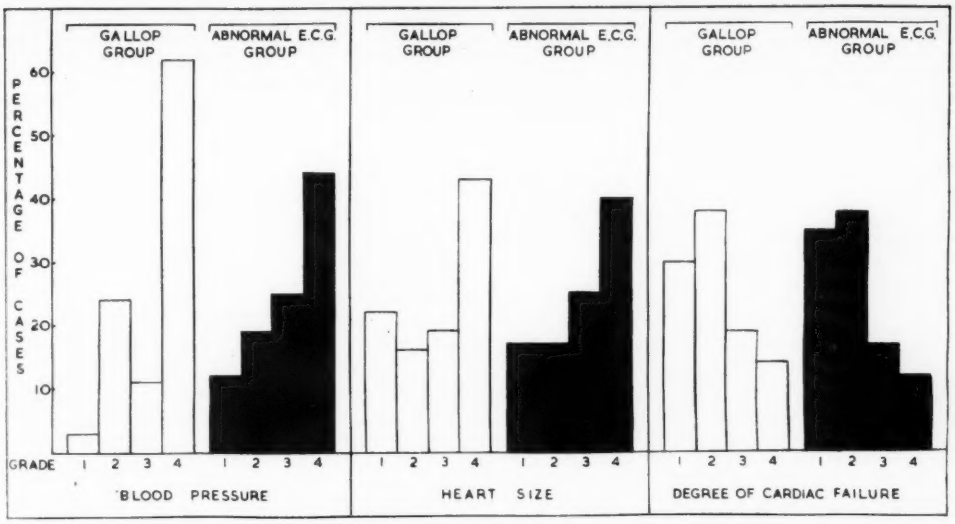


FIG. 3.—The clinical findings as regards blood pressure, heart size, and degree of cardiac failure are shown to be similar in the gallop rhythm group (37 cases) and the abnormal electrocardiogram group (52 cases).

minate gallop. It would, however, be rash to assert that right-sided gallop always arose in the right ventricle. Contrary to the findings of Evans (1943), none of the auricular gallop sounds was most audible near the xiphisternum.

SUMMARY

Gallop rhythm as defined was heard and recorded phonocardiographically in 37 of 100 patients with hypertension.

Poor correlation was shown between gallop rhythm and the degree of heart disease as judged by blood pressure, heart size, degree of cardiac failure and electrocardiographic abnormality.

It is suggested that gallop rhythm has little value in prognosis, as it occurs in a wide range of clinical circumstances.

A tendency was shown for " rapid filling " gallop to be associated with right-sided cardiac failure.

This paper is taken from a Cambridge M.D. thesis. I wish to thank Professor F. H. Smirk for the generous provision of facilities in his Department at Otago University, and to Professor E. P. Sharpey-Schafer and A. C. Dornhorst for helpful criticism.

REFERENCES

Ducrosal, P. (1932). *Amer. Heart J.*, **7**, 613.
Evans, W. (1943). *Brit. Heart J.*, **5**, 205.
Frost, J. (1949). *Acta. med. Scand.*, **133**, 268.
Garvin, C. F. (1943). *Amer. J. med. Sci.*, **205**, 814.
Holt, E. (1927). *Amer. Heart J.*, **2**, 453.
Lian, C., Minot, G., and Welti, J. J. (1941). *Phonocardiographie Auscultation Collective*, Paris.
Miles, B. E. (1950). *M.D. Thesis*, Cambridge.
Orías, O., and Braun-Menéndez, E. (1939). *The Heart Sounds in Normal and Pathological Conditions*. 1st ed., London.
Rappaport, M. B., and Sprague, H. B. (1942). *Amer. Heart J.*, **23**, 591.
Wolferth, C. C., and Margolies, A. (1931). *Med. Clin. N. Amer.*, **14**, 897.

PERIPHERAL CIRCULATORY CHANGES ASSOCIATED WITH ARTERIOVENOUS ANEURYSMS

BY

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During recent years several investigations into the circulatory disturbances found with an ateriovenous fistula have been reported. Measurements of blood flow distal to arteriovenous fistulæ in man have been reported by Lewis and Drury (1923), Lewis (1940) and Cohen *et al.* (1948). In the two cases reported here, attention has been directed chiefly to the mechanism of the adjustment of the blood supply to the tissues distal to the fistulæ, as conflicting views have been expressed on this point (Holman, 1949). In the first case the fistula was in the deep femoral vessels and in the second, in the vessels of the thenar eminence of the hand. Both situations afforded favourable opportunities for the investigation of the distal circulation.

Methods of Investigation of the Peripheral Circulation

In the first case, the blood flow through the foot was determined in a venous occlusion plethysmograph filled with water maintained at 44° C. The foot was kept in the instrument at this temperature for 45 minutes before observations were begun. This ensured full local vasodilatation and the tracings thus afforded a measurement of the maximal blood flow as defined by Kunkel and Stead (1938). The foot was kept at approximately heart level as no local venous engorgement was present and satisfactory inflow tracings were obtained at this height.

In the second case, the blood flow through the terminal two phalanges was measured in a calorimeter constructed on the principles described by Greenfield and Scarborough (1949) and Greenfield and Shepherd (1950). The tip of the finger being examined was supported on an adjustable platform, and it was thus possible to measure corresponding parts of each finger. The heat elimination was expressed as cal./min./ml. of finger tissue. The observations were made with the water in the calorimeter between 28° and 30° C but all the results have been expressed by the method of Cooper *et al.* (1949) as the rate of elimination of heat into water at 32° C. The calorimetric method of measuring blood flow was chosen in preference to a finger venous occlusion plethysmograph as the venous pressure on the affected side was considerably elevated and the venous bed could not be effectively emptied by raising the hand. Under these circumstances it would not have been possible to obtain reliable arterial inflow tracings, especially as observations were required at full vasodilatation which in itself leads to rapid filling of the venous bed.

The systolic arterial pressure in the finger was obtained by the method described by Gaertner (1899). A small cuff was fitted over the proximal phalanx and, after exsanguinating the finger with a tight rubber bandage, was inflated above brachial systolic pressure. The bandage was removed and the pressure in the cuff was slowly reduced till a sudden flush of inflowing blood was observed in the finger tip. The pressure at this point was read as the digital arterial systolic pressure. A modification of this method was used for the determination of the blood pressure in the legs. The lower limbs were soaked in water at 43° C for 15 minutes to ensure dilatation of the cutaneous

vessels. The legs were then elevated to blanch the skin and a cuff 20 cm. in breadth was applied and inflated to above systolic pressure. The limbs were replaced in the water and the pressure was slowly reduced until the flush of reactive hyperæmia was observed in the feet. No reliable readings of diastolic pressure could be made using the cuff as described by Mendlowitz (1938) since the point at which throbbing disappeared could not be ascertained on the side with the fistula.

Case Reports and Circulatory Measurements

Case 1. A male, aged 38 years, was wounded in the right lower limb in March, 1944. Since then he has been aware of a swelling and throbbing in the right groin which have gradually increased. There has been no swelling of the distal part of the limb and apart from an increased liability to chilblains in the right foot there has been no disability.

On examination a pulsatile swelling with a marked thrill was present immediately below the right inguinal ligament in the line of the femoral artery. The thrill was readily abolished by local compression of the artery. The dorsalis pedis and posterior tibial pulses were present on both sides, but were abolished on the right side when the fistula was closed. No dilated veins were seen. The skin of the feet appeared healthy and there was no hypertrophy of the affected limb. After exposure of the feet in the laboratory at 19° C there was no difference in temperature between the two sides. There was clinical and radiological evidence of left ventricular enlargement. No abnormalities were detected in the other systems.

A surgical exploration was carried out by Mr. Clifford Jones and an arteriovenous fistula between the profunda femoris artery and vein close to the main artery was excised. The arteries immediately proximal and distal to the fistula were conspicuously enlarged.

Circulatory changes on closure of the fistula. The fistula was readily closed by pressure over the artery in the groin. The resulting changes in pulse rate, blood pressure in arm and legs and maximal blood flow in the feet are shown in Table I. They represent the averages of several observations which were uniformly consistent.

TABLE I

Circulatory Changes Associated with Closure of the Arteriovenous Fistula in Case 1

	Fistula open		Fistula closed	
Pulse rate per minute	76		57	
Blood pressure in left arm in mm. Hg.	135/80		150/98	
	Right	Left	Right	Left
Systolic blood pressure in legs in mm. Hg.	75	115	55	125
Maximal blood flow in feet in ml./min./100 ml.	14·8	13·2	7·2	17·2

Pulse rate and brachial blood pressure. The fall in pulse rate and elevation of the general arterial pressure were similar to those described in previous accounts of fistulæ between these vessels (Holman, 1923; Laplace, 1935). Certain additional features were also observed electrocardiographically in association with these changes. Immediately after closure of the shunt and coincidental with the bradycardia a lengthening of the P–R interval was consistently seen. With the fistula open the interval was 0·16 sec. and this increased to 0·30 sec. when it was closed (Fig. 1). The character of the P waves also altered and they became flatter in all leads and inverted in lead III. There were no changes in the ventricular complexes in either the standard or unipolar leads. In this subject similar changes were produced by digital compression of the right carotid sinus while the fistula was open. In experiments where the closure of the fistula was maintained over a period of a minute a continuous electrocardiogram showed that the changes were most pronounced in

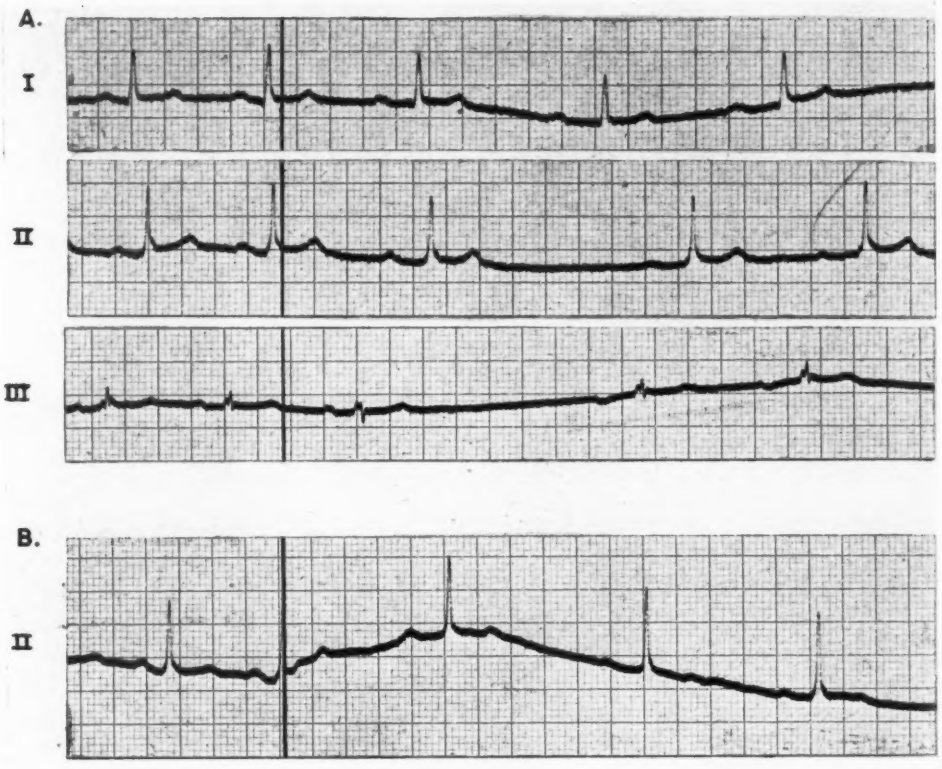

FIG. 1.—Electrocardiograms showing the effect of closing the fistula and of right carotid sinus pressure in Case 1. (A) Leads I, II, and III. Closure of the fistula at the point marked by the vertical line produced lengthening of the P–R interval, flattening or inversion of the P waves and cardiac slowing. (B) Lead II. Compression of the right carotid sinus produced similar changes.

the first few seconds. Thereafter the heart rate increased slightly, the P–R interval decreased and the P waves became more normal even though complete closure was apparently maintained. These results are consistent with the view that the changes were mediated through the vagus as a depressor reflex in response to the raised arterial pressure.

Peripheral circulatory changes. The alterations in the blood pressure and blood flow in the lower limbs were of considerable interest. With the fistula open the arterial pressure on the affected side was considerably less than on the normal side. Nevertheless, in spite of this reduced pressure, the maximal blood flow in the right foot was slightly greater than on the opposite side. These results indicated that an enlargement of the arteries had occurred in the foot on the side of the fistula to maintain the distal blood flow at this high level. Closure of the fistula produced different effects on the two sides. The increase in blood flow on the normal side was probably due to the rise in general arterial pressure, as under the experimental condition of full dilatation due to local heat it could not be attributed to a further release of vasoconstrictor tone. The femoral artery on the affected side was inevitably occluded when the fistula was closed and consequently there was a decrease in both distal blood pressure and blood flow.

The validity of the plethysmographic method in making these measurements must be considered, especially on the side where the arterial pressure was greatly reduced. The pressure as measured

with a cuff 20 cm. in width was 75 mm. of mercury. It was possible that the venous occlusion cuff of 4 cm. in width might reduce the arterial inflow to the foot but comparison of inflow tracings with venous occlusion pressures of 70 and 50 mm. showed no significant differences and on this evidence it was thought that the narrow venous occlusion cuff did not interfere materially with the arterial inflow. Obviously any error would be in the direction of an underestimation of the blood flow on the affected side and this would not alter the conclusion that the arteries distal to the fistula were considerably enlarged.

Case 2. A female, aged 34 years, had first noticed in February, 1947, a swelling at the base of the left thumb which slowly increased in size and began to pulsate. The veins above the wrist became grossly distended. The onset was gradual and she was unaware of any injury to the region. A diagnosis of an arteriovenous fistula was made and a surgical exploration was carried out in July, 1947. The fistula was not found and the radial artery was ligated at the wrist. In 1948 arteriography was twice attempted without success. After the second occasion the thumb, index and middle fingers became blue and cold owing to the development of arterial thrombosis. Subsequently, their condition slowly improved but they have always become excessively cold on exposure.

FIG. 2.—The left hand showing the swelling of the arteriovenous aneurysm in the thenar region and the dilated veins in the forearm.

On examination there was a firm smooth swelling in the thenar region of the left hand from which dilated veins ran proximally up the forearm (Fig. 2). These veins showed a distinct slight pulsation. After exposure for half an hour to ward temperature (19° C) the thumb, index and middle fingers were cyanosed and colder than the other fingers of the left and right hands which were of equal temperature. A left radial pulse was distinctly felt in spite of the previous ligation, and a strong ulnar pulse was also present. A loud, prolonged systolic murmur was audible over these arteries and over the thenar swelling. Strong brachial arterial pulsations were palpable and a thrill and murmur were present over the whole length of the vessel. Apart from the local changes in the hand the limbs were of equal size. A radiograph of the hands showed no difference in structure between the bones. There was no clinical or radiological evidence of cardiac enlargement.

The clinical diagnosis was an arteriovenous aneurysm in the left thenar region with thromboses in the arteries supplying the thumb, index and middle fingers. As the nature and extent of the fistula were uncertain, comparative observations were made in the first place to determine whether the fistula could be adequately closed by local pressure.

Z

Pulse rate and brachial blood pressure. With the circulation to the left hand excluded by a cuff the heart rate consistently slowed. Numerous counts made by several different observers showed that the slowing was consistently in the range of 3 to 6 beats a minute. The average pulse rate was 72 and this fell to 68 when the cuff was inflated. Digital closure of the fistula gave a similar result. The average right brachial arterial pressure with the circulation free was 110/68 and with the left-arm cuff inflated the pressure was 110/74. The alteration in pressure was most convincingly demonstrated by maintaining the right arm sphygmomanometer at 70 mm. At this level sounds were loudly heard with the flow through the arteriovenous aneurysm unchecked, but on stopping the flow either by inflating the left-arm cuff or by digital pressure the sounds promptly disappeared. The electrocardiograms taken in association with these changes were normal and only cardiac slowing was seen on closing the fistula.

Venous blood oxygen. Samples of blood were taken from a dilated vein at a point 12 cm. above the fistula without proximal venous congestion. The first specimen was withdrawn with the fistula open. The fistula was then closed by digital pressure, the hand was elevated to empty the venous bed and then lowered to below heart level, pressure still being maintained over the fistula. After a further two minutes rest, a second specimen of blood was withdrawn. The blood was analysed in the manometric Van Slyke apparatus with the results given below.

	Vols. oxygen/100 ml. blood	Percentage saturation
Specimen 1. Fistula open.	15·8	96
Specimen 2. Fistula closed.	11·8	72
Mixed 1 and 2. Saturated.	16·4	100

Venous Pressure. Measurement was made in a dilated vein at a point 8 cm. proximal to the fistula by the direct method using a citrate manometer. The limb was maintained at approximately heart level with the patient lying flat and the pressures are expressed in relation to the sternal angle. With the fistula open the average reading was +19 cm. Unusually large pulsations were observed in the manometer. On digital closure of the fistula in repeated experiments, the pressure fell rapidly to approximately +8 cm.

It was concluded that all these observations indicated that digital pressure effectively shut the arteriovenous aneurysm and that an investigation of the distal circulation might be carried out using this method of closure.

Capillary Pulsation. After soaking both hands in water at 43° C. for 15 minutes the finger tips and nail beds were inspected for capillary pulsation. This was readily seen in all the right-hand fingers and was not appreciably altered by opening and closing the fistula. In the left hand it was observed in the ring and little fingers to a slight degree with the fistula open, and conspicuously with the fistula closed. No pulsation was seen in the index or middle fingers with the fistula either open or closed, results consistent with the presence of thrombosis in their digital arteries.

Digital arterial pressure and blood flow. The results obtained in all the fingers of both hands are shown in Table II. The investigations were performed at least in duplicate and were consistent on the separate occasions. The measurements were all made at full reflex vasodilatation obtained by immersing the feet in stirred water at 43° C. The observations were not begun until the patient was sweating freely and the heat elimination had reached a steady high level.

In the right fingers the systolic pressure was not significantly affected by closing the fistula but the blood flow as reflected by the heat elimination always rose slightly. The average increase was 12 per cent and this was attributed to the rise in general diastolic pressure. Pressure of an equal degree on the left hand other than over the fistula did not alter the blood pressure or flow.

In the left hand the digital pressures with the fistula open were conspicuously reduced in comparison with the right hand; on closure of the fistula they all rose to a height comparable with that in

TABLE II

ARTERIAL SYSTOLIC PRESSURE AND HEAT ELIMINATION OF THE FINGERS MEASURED AT FULL REFLEX VASODILATATION

Finger		Fistula open		Fistula closed	
		Blood Pressure (mm. mercury)	Heat elimination (cal./min./ml.)	Blood Pressure (mm. mercury)	Heat elimination (cal./min./ml.)
Index	right	75	2·2	78	2·5
	left	36	0·3	80	0·5
Middle	right	82	2·3	82	2·4
	left	40	1·5	80	2·0
Ring	right	79	2·5	83	2·8
	left	40	2·6	82	4·3
Little	right	81	2·2	87	2·6
	left	40	1·9	83	3·4

the normal hand. These differences were also readily demonstrated by deflating the cuff pressure on the left third, fourth, or fifth fingers to any level between 45 mm. and 80 mm. with the fistula open. The fingers remained blanched but on compression of the fistula immediate flushing occurred. In the left index finger the pressures both with the fistula open and closed were consistently slightly lower than in the other fingers of the left hand. It will be seen that in all the fingers the systolic arterial pressure approximately doubled on closing the fistula.

The changes in blood flow in the left hand were equally striking. In the index finger the heat elimination was exceptionally low in comparison with the corresponding normal right finger. The heat elimination in the left middle finger was also significantly reduced, though not to such a conspicuous degree. The low results were attributed to the previous arterial thrombosis. In both these fingers there was a great relative increase in blood flow on closing the fistula. In the left ring and little fingers the heat eliminations with the fistula open were similar to those of the corresponding fingers of the normal hand. On closure of the fistula, however, there was a great increase in the heat elimination to a level considerably above that obtained in the contralateral fingers. The actual readings obtained in one representative experiment involving the ring fingers is shown in Fig. 3. The average increase in heat elimination of all the fingers resulting from closure of the fistula was 61 per cent. Digital pressure on the aneurysm caused some discomfort but it was shown that an equal degree of pressure on the right thenar eminence did not alter the blood flow through the left fingers. The effect of pressure on an artery proximal to the fistula was determined by digital occlusion of the left radial artery while the heat elimination from the left ring finger was being measured: the freely pulsating ulnar artery was left unobstructed. This experiment shows that the blood flow through the ring finger was decreased (Fig. 4).

The results of the circulatory measurements in this case, as in the first case, demonstrated clearly that there was a persistent enlargement of the arteries unaffected by thromboses distal to the fistula. In spite of the disparity in digital blood pressures with the fistula open the blood flows were approximately equal on the two sides. With the fistula closed the pressures were similar but the blood flows were considerably greater than normal on the affected side.

DISCUSSION

The arteriovenous fistula in the first case was traumatic in origin but the exact nature of the lesion in the second was difficult to determine. An injury or bruise not causing penetration of the skin may be the apparent starting point of an arteriovenous shunt (Reid, 1925*b*) but the patient was

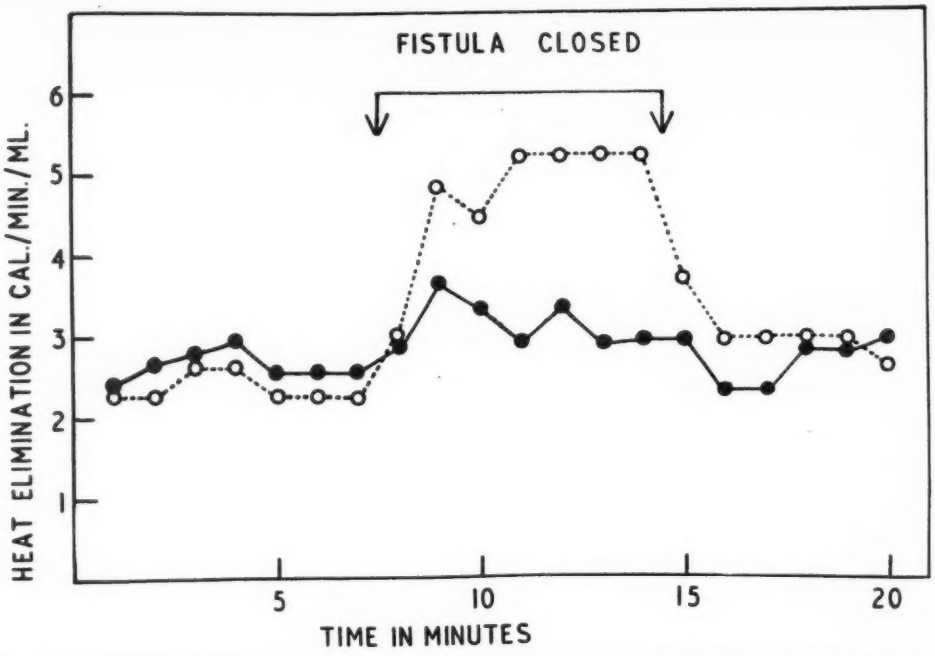

FIG. 3.—The effect of digital closure of the arteriovenous fistula on the heat elimination of the index fingers; right ●———●, left o———o. The blood flows at full reflex vasodilatation were similar on the two sides with the fistula open. Closure of the fistula led to a slight increase on the normal side and a greater increase on the side of the fistula.

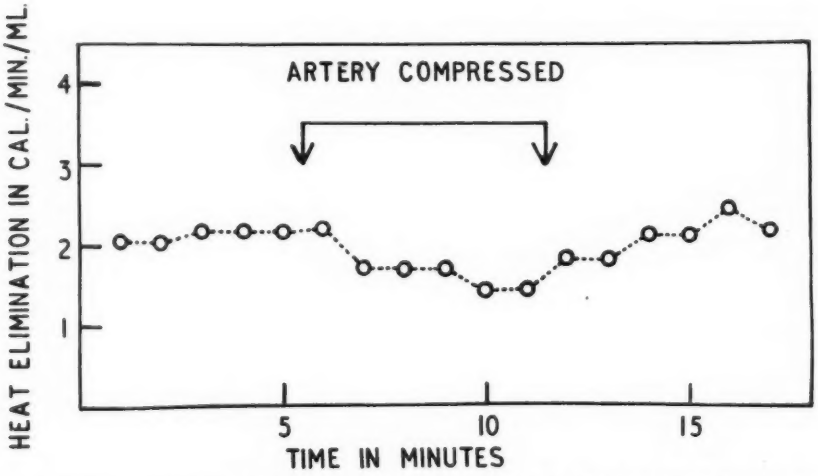

FIG. 4.—Compression of the radial artery immediately proximal to the fistula led to a decrease in the heat elimination of the left ring finger.

unable to recollect any trauma. The condition was thus apparently of congenital origin, in spite of her age at its onset. Several cases of congenital arteriovenous aneurysms in the hand have been reported (Callander, 1920; Reid, 1925*a*; Pemberton and Saint, 1928; Horton, 1932) and occasionally the abnormality has not been noted until adult life (D. D. Lewis, 1930; Horton and Ghormley, 1933). The absence of cardiac enlargement and of hypertrophy of the limb is consistent with the view that the fistula is small and not of longer duration than the history suggests.

The blood flow measurements in the first case were similar to those previously recorded by Lewis and Drury (1923), Lewis (1940) and Cohen *et al.* (1948). In their cases of over two years duration, and thus comparable to the two reported here, the blood flow on the affected side was either similar to, or greater than, that on the normal side. Closure of the fistulæ always led to a decrease in the distal blood flow but the fistulæ involved the main limb vessels and the change in the distal arterial pressure was not ascertained. In the second case reported here with the fistula in the thenar eminence the collateral arteries were not occluded when the fistula was closed. The distal pressure increased to normal and the blood flow rose to considerably above normal. These results resemble those described by Robertson *et al.* (1950) who in experiments on dogs found that occlusion of an arteriovenous shunt increased the blood flow to the distal part of the extremity between 40 and 210 per cent and that this was associated with a considerable rise in the distal arterial pressure.

The enlargement of the arteries distal to an arteriovenous fistula is of considerable interest. The dilatation in the neighbourhood of the aneurysm is probably the direct result of distension by an increased volume of blood flowing to the shunt as suggested by Holman (1949). This mechanism may also account for the enlargement immediately distal to the aneurysm where there is a retrograde flow of blood. The enlargement of the arteries in the foot and the fingers in the two cases described cannot, however, be explained in this manner. They are not concerned in carrying blood to the fistulæ and the pressure within them cannot have caused any undue distension. In fact they have enlarged in spite of the greatly reduced pressure distal to the fistula and it appears that the necessary adjustment of blood flow is not effected by purely mechanical means. However, the suggestion of Lewis (1940) that a chemical substance originating in ischæmic tissue is responsible for the distal dilatation may apply in these circumstances. The greatly reduced arterial pressure will adversely affect filtration of fluid in the capillaries and, even though the volume of blood flow is normal, tissue nutrition may be inadequate. This may account for the recurrent cutaneous lesions in the first case in spite of the large blood flow. It may also explain the increase in distal blood flow to above normal levels in very long-standing cases of arteriovenous aneurysm.

With regard to treatment, the dangers associated with interference with the proximal arterial supply have long been recognized (Reid, 1925*c*) and have been amply demonstrated in the second case in which compression of the radial artery immediately proximal to the fistula reduced the blood flow to the medial fingers even though a large pulsating ulnar artery was present. The fistula, constituting a site of low resistance, had the first claim on the blood flow and an attempt to reduce its supply merely led to deviation of blood from the tissues to maintain the flow through the shunt. Furthermore, proximal interference will reduce even lower the blood pressure distal to the fistula and it is not surprising that thrombosis in this region is a recognized consequence of this procedure (D. D. Lewis, 1930; Wilbur, 1930). It is clear from the physiological studies that the only satisfactory solution is complete extirpation of the fistula, as in the first case. This operation is often fraught with great technical difficulties, especially in the congenital cases, and has not again been attempted in the second case.

Summary

Two cases of arteriovenous fistula have been described with particular reference to the peripheral circulation and the condition of the arteries distal to the fistula.

In the first case the fistula was between the deep femoral vessels and was of six years' duration.

Closure of the fistula produced considerable cardiac slowing and rise in blood pressure. These changes were associated with a lengthening of the P–R interval and abnormalities in the P waves attributed to excessive vagal activity. The blood pressure in the limb distal to the fistula was considerably reduced but the blood flow in the foot was slightly greater than on the normal side.

In the second case the fistula was situated in the thenar region of the hand and was of three and a half years' duration. A relatively slight decrease in heart rate and increase in diastolic pressure on checking the flow through the fistula showed that it was small. In the fingers on the affected side with patent digital arteries, the blood pressure with the fistula open was greatly reduced but the blood flow was similar to that on the normal side. Closure of the fistula increased the blood pressure to that on the normal side and the blood flow to above the normal.

These changes in the circulation indicated a persistent enlargement of arteries supplying tissues distal to the aneurysms. As the pressure in these arteries was unduly low and they were not concerned with the supply of blood to the fistulæ the enlargement could not be attributed to mechanical causes. The features were consistent with the hypothesis of Lewis that the enlargement was due to locally formed metabolites.

Occlusion of an artery immediately proximal to a fistula resulted in a deviation of blood from the distal tissues to the fistula and illustrated the dangers associated with interference with the proximal arteries. The only satisfactory treatment is complete extirpation of the fistula.

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References

Callander, C. L. (1920). *Johns Hopkins Hosp. Rep.*, **19**, 259.
Cohen, S. M., Edholm, O. G., Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1948). *Clin. Sci.* **7**, 35.
Cooper, K. E., Cross, K. W., Greenfield, A. D. M., Hamilton, T. McK., and Scarborough, H. (1949). *Ibid.*, **8**, 217.
Gaertner, G. (1899). *Wien. klin. Wschr.*, **12**, 696.
Greenfield, A. D. M., and Scarborough, H. (1949). *Clin. Sci.*, **8**, 211.
——, and Shepherd, J. T. (1950). *Ibid.*, **9**, 323.
Holman, E. (1923). *Arch. Surg.*, **7**, 64.
—— (1949). *Surgery*, **26**, 889.
Horton, B. T. (1932). *J. Amer. med. Ass.*, **98**, 373.
——, and Ghormley, R. K. (1933). *Proc. Mayo Clin.*, **8**, 773.
Kunkel, P., and Stead, E. A. (1938). *J. clin. Invest.*, **17**, 715.
Laplace, L. B. (1935). *Amer. J. med. Sci.*, **189**, 497.
Lewis, D. D. (1930). *Lancet*, **2**, 621.
Lewis, T. (1940). *Clin. Sci.*, **4**, 277.
—— and Drury, A. N. (1923). *Heart*, **10**, 301.
Mendlowitz, M. (1938). *Clin. Sci.*, **3**, 387.
Pemberton, J. de J., and Saint, J. H. (1928). *Surg. Gynec. Obstet.*, **46**, 470.
Reid, M. R. (1925*a*). *Arch. Surg.*, **10**, 601.
—— (1925*b*). *Ibid.*, **10**, 997.
—— (1925*c*). *Ibid.*, **11**, 237.
Robertson, R. L., Dennis, E. W., and Elkin, D. C. (1950). *Surgery*, **27**, 1.
Wilbur, D. L. (1930). *Amer. J. med. Sci.*, **180**, 221.

THE HEART IN MYOTONIA ATROPHICA

BY

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The sudden and unexpected death from heart failure of a man suffering from myotonia atrophica prompted this enquiry. No evidence of grave heart disease had been detected, though looked for, but the patient (Case 1) died suddenly from what was probably acute left ventricular failure while in bed in hospital during investigation of his neurological disorder. Post mortem there was no cardiac abnormality apart from ventricular dilatation but the A-V bundle was not examined.

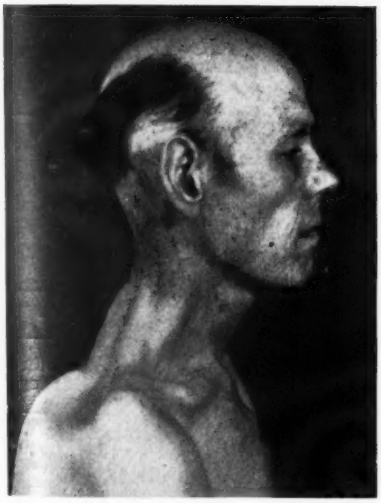

FIG. 1.—Case 1. Duration of symptoms fifteen years; longest in this series. He died suddenly and unexpectedly of acute heart failure. Contrast gross neurological features with slight changes in cardiovascular system (Table II).

It was the experience of Evans (1944) after studying 13 cases that " signs discovered during the examination of the cardiovascular system contribute to the surer and earlier diagnosis of myotonia atrophica." He pointed out that the pulse is often small (8 out of 13), the blood pressure is sometimes low (5 out of 13), and the first heart sound in the mitral area commonly shows impurity and/or splitting (10 out of 13). Changes that commonly characterize the electrocardiogram include prolongation of the P–R period (10 out of 13 greater than 0·20 sec.), low voltage of the P wave (8 out of 13), or notching of the QRS complex (9 out of 13) and left axis deviation (7 out of 13). Evans noted that neither the age of the patient, the duration of symptoms (over five years in 5; no other details given), nor their severity appeared to determine the presence of cardiographic abnormalities.

As Evans pointed out, there is little reference in the English literature to involvement of the heart in myotonia. Adie and Greenfield (1923), who reported the first post-mortem study of the disease in this country, mentioned that a slow heart rate had been observed in isolated cases (Griffith, 1912; Röhrer, 1916; Maas and Zondek, 1920), but in the one case examined with the electrocardiogram the P–R interval was normal (0·16 to 0·17). Thaysen (1943) found electrocardiographic reports in 30 of the published cases of the disease; in 13 the P–R interval was prolonged. The additional available evidence on the subject is summarized in Table I. In the majority of these reports it can be inferred that the disease was well established when the cardiac changes were noted. In some cases insufficient evidence is published.

In the present series of 16 cases the following cardiovascular abnormalities were noted (Table II). The pulse was small in six, and slow (50) in two cases. The blood pressure was raised in one case; the systolic pressure was never below 100, but was between 100 and 110 in seven cases. There was

TABLE I

PUBLISHED REFERENCES TO THE HEART IN MYOTONIA ATROPHICA

Cardiovascular changes	No. of cases	Reference
Cardiac enlargement (1); prolonged P–R interval (3)	3	Maas and Zondek, 1920.
Sinus bradycardia (1)	1	Havier and Decourt, 1933.
P–R interval slightly prolonged (2); left axis deviation (1)	7	Guillain and Rouques, 1932.
Hypotension (3); prolonged P–R interval (2)	3	d'Antona, 1935.
P–R interval normal (6)	6	Kolb *et al.*, 1938.
Prolonged P–R interval and inverted T1 (1)	1	Mondon and Pasquet, 1939.
Bradycardia (4); hypotension (5); systolic murmur (2); low P waves (1 of 8); prolonged P–R interval (4 of 8); bundle branch block (1 of 8); left axis deviation (2 of 8); E.C.G. normal (2 of 8)	13	Waring *et al.*, 1940.
Low P waves; prolonged P–R interval; notched QRS; left axis deviation (2)	3	Carrillo, 1941.
No abnormality	11	Segura and Lanari, 1941.
Bradycardia; low P waves; prolonged P–R interval; T3 inverted (1)	1	Carrot *et al.*, 1943.
See text	13	Evans, 1944.
Prolonged P–R interval (3); auricular flutter (2)	4	Biörck and Nylin, 1944.
Bradycardia (4); tachycardia (1); prolonged P–R interval (3); left axis deviation (3)	8	Ask-Upmark, 1944.
Auricular flutter and A-V dissociation (1)	1	Broustet *et al.*, 1945.
Bradycardia (1); faint heart sounds (2); low B.P. (3); heart size normal (3); E.C.G. normal (2)	3	Black and Ravin, 1947.
Bradycardia "some cases"; B.P. usually "somewhat low"; heart sounds normal in all. Radioscopy in 5—normal. Low P waves (1 of 12); prolonged P–R interval (3 of 12)	101	Thomasen, 1948.

TABLE II

THE CARDIOVASCULAR CHANGES IN SIXTEEN CASES OF MYOTONIA ATROPHICA

Case No.	Age in years	Duration of symptoms (years)	Pulse		B.P.	1st heart sound	Size of heart*	Electrocardiographic changes			
			Rate	Character				Voltage of P wave	P–R interval	QRS	Other changes
1	51	15	65	small	100/70	N.	+	low	0·16	N.	L.A.D.
2	48	8	65	N.	135/75	split	N.	low	0·21	sl.†	L.A.D.
3	39	11	75	small	110/70	N.	N.	N.	0·21	N.	—
4	49	10	95	small	110/80	N.	N.	low	0·18	N.	—
5	26	10	65	small	110/70	split	N.	low	0·18	sl†	—
6	37	3	50	small	120/70	split	N.	N.	0·20	N.	Ex S††
7	52	2	80	N.	110/80	impure	N.	N.	0·21	N.	—
8	39	10	65	N.	110/70	N.	N.	low	0·20	N.	L.A.D.
9	41	12	85	N.	120/85	N.	++	low	0·22	N.	L.A.D.
10	40	9	58	N.	120/70	split	N.	N.	0·21	N.	—
11	43	10	60	small	115/80	split	N.	low	0·24	N.	T in V1
12	24	1	72	N.	105/75	N.	N.	N.	0·16	N.	—
13	40	½	70	N.	115/80	N.	N.	N.	0·18	N.	—
14	48	?	80	N.	155/90	N.	N.	N.	0·18	N.	Ex S††
15	48	10	70	N.	130/80	N.	N.	N.	0·17	N.	—
16	29	3	50	N.	130/95	N.	N.	low	0·16	N.	—

* + indicates slight, and ++ moderate enlargement.
† Sl. indicates slurred.
†† Extrasystoles.

splitting of the first heart sound in the mitral area in five cases; in one this sound was impure. The electrocardiogram showed low voltage of the P waves in eight; in the first lead the voltage of the P wave was always low. The P–R interval was more than 0·20 sec. in six, and less than 0·20 sec. in eight cases. Slurring of the QRS complex was present twice. In four cases there was left axis deviation.

Radioscopy revealed a normal heart outline in thirteen patients. In Case 7 the heart was small; in Cases 1 and 9 there was slight and moderate enlargement respectively. Case 14 had recently suffered from myxœdema with considerable cardiac enlargement; treatment with thyroid had reduced the heart to normal size and produced corresponding clinical improvement. Low basal metabolic rates have been reported in myotonia atrophica but Thomasen (1948) stated that myxœdema has not been described as a complication of myotonia atrophica. He commented on the frequency of myotonic phenomena and muscular hypertrophy in myxœdema.

These findings are in general agreement with those described by Evans. Where abnormalities were observed they corresponded in character with those he described. A small pulse, a relatively low blood pressure, and splitting of the first heart sound are frequent findings in this disease. The electrocardiogram frequently reveals low P waves and a prolonged P–R interval. Quinine (10 grains t.i.d.) did not influence these signs although it frequently reduced the myotonia.

Such findings are interesting and indicate that involvement of the heart should be considered in myotonia atrophica. But their value in the *early* diagnosis of the disease, as claimed by Evans, is open to question. It certainly cannot be deduced from a study of this series. In ten of the sixteen cases symptoms were present for eight years or more. In only six (Cases 6, 7, 12, 13, 14 and 16) could it be said that the disease was in an early stage. In Case 14 (a brother of Case 7) the duration of the disease could not be assessed as he had also been suffering from myxœdema. In the remaining " early " cases symptoms had been present for three years, two years, one year, six months, and three years respectively. In Cases 12 and 13 the heart was normal. In Case 7 the only abnormalities were an impure first heart sound, a small heart and a P–R interval of 0·21 sec. In Case 6 there was a slow pulse (50), splitting of the first heart sound, and a P–R interval of 0·20 sec. In Case 16 the pulse was slow (50) and the P waves low in all leads. Thus, of five " early " cases of this disease the heart was normal in two; in the remaining three the amount of cardiac abnormality was not great. By contrast, the neurological abnormalities in these five cases were considerable. They readily provided a diagnosis.

Case 6. Man, aged 37 years. Symptoms were of three years duration. He had not been able to do his work for one year (light labourer). He complained of increasing muscular weakness. There was atrophy of the neck muscles and of the calf muscles with complete areflexia and characteristic myotonia. The latter was observed in the tongue, the muscles of the hands and forearms and of the eyelids. There was evidence of personality and intellectual deterioration.

Case 7. Man, aged 52 years. Symptoms of two years duration. He gave up his work in a foundry eighteen months previously on account of increasing weakness and pains in his limbs. He took up light work on a farm. He was bald, the testicles were atrophied, and there was marked generalized muscular weakness. His voice was weak and he had difficulty in swallowing. Considerable wasting of the calf and peroneal muscles. Myasthenic facies, absent deep reflexes, myotonia of the hand muscles, and typical atrophy of the neck muscles.

Thus, in both these patients, despite the relatively short duration of *symptoms* the features of the disease could be readily discerned. It is well known of course that apparently healthy members of a diseased family may show typical *signs* of the disease.

Case 12. Man, aged 24 years. Duration of symptoms one year. Increasing myotonia had made it difficult for him to load and fire a rifle. Relaxation of grip was becoming troublesome to execute. There was complaint of slight weakness of the arms but his legs were normal. Myotonia of the hands and wasting of both sternomastoid muscles were the only abnormalities but they were considerable. They sufficed to make the diagnosis.

Case 13. Man, aged 40 years. Duration of symptoms was six months. The only complaints were of weakness and easy fatigue of arms and legs. The weakness was especially troublesome about the neck and shoulders. Yet he showed the characteristic dull and lifeless expression with the heavy eyelids and the

flabby lips (Fig. 2). The cervical muscles were wasted and weak. Typical myotonic phenomena were demonstrated in his hands and forearms.

Case 16. Woman, aged 29 years. Weakness had begun three years ago but wasting had not previously been detected. She had been incorrectly diagnosed as an example of ankylosing spondylitis but the classical features of myotonia atrophica were readily recognizable.

These cardiac changes were not observed in unaffected members of a family. Ten healthy relatives (nine in the same generation as the diseased members) of some of the above patients were examined. In all ten the electrocardiographic tracings were normal. In one family, only the one unaffected member had a normal electrocardiogram. Unfortunately, in this series there are few young healthy relatives, long-term observation of whom would be helpful in determining the time of onset of the cardiac changes.

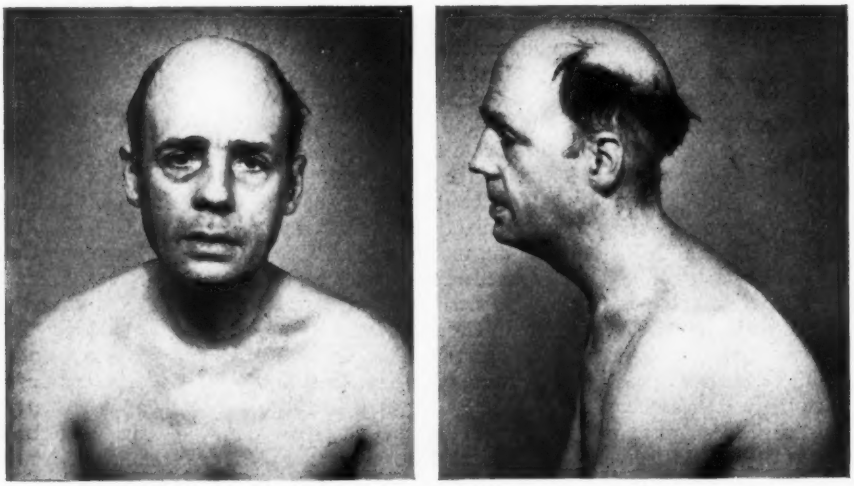

FIG. 2.—Case 13. Duration of symptoms six months; shortest in this series. Yet the signs of the disease can be recognized by the facial appearance and thin neck muscles. The heart was normal.

No doubt the rate and mode of progress of this polysymptomatic disease vary considerably. One finds on the one hand relatively symptomless patients with some of the hallmarks of the disease (premature baldness, wasting of the neck muscles, myasthenic expression) and on the other hand patients in whom mental deterioration and myotonia antedate the other features. When there is much muscular wasting there are always some mental changes, but the reverse is not necessarily true.

Each patient in this series was photographed and it is apparent that a typical example of the disease can hardly fail to be identified by the appearance of the face and neck alone. Indeed, quick recognition of the nature of the malady is probably a commoner experience than diagnosis arrived at by formal examination. The dull apathetic expression, the heavy eyelids, the hollow temples, and the loose mouth, with the characteristic wasting of the masseters and the sternomastoid muscles, are the distinctive signs that catch the eye. The profile view of the patient presents no less striking an appearance. It is then that one sees the true extent of the wasting of the neck muscles with the prominent larynx and the curve forward of the neck.

Cardiac abnormalities are not found in myotonia congenita. In other more common types of muscular dystrophy the majority of observers have found no frequent or characteristic clinical changes in the heart. In myasthenia gravis also the heart is usually normal.

Summary and Conclusions

Examination of the heart in 16 cases of myotonia atrophica confirms previous reports that it is frequently involved in the disease.

A small pulse, a relatively low blood pressure, and splitting of the first heart sound in the mitral area are frequent clinical findings. The electrocardiogram may reveal low P waves and prolongation of the P–R interval.

The heart is usually normal in size.

In my experience, however, these cardiac changes may not be present when the neurological features of the disease are already established. In the two patients with the shortest duration of symptoms the heart was normal. In three further patients with relatively short duration of symptoms the cardiac abnormalities were not remarkable. In the remaining patients the disease was of long standing and some or all of the above-mentioned cardiac changes were commonly found.

The neurological features of this disease develop earlier and are more readily identified than the cardiological signs.

References

Adie, W. S., and Greenfield, J. G. (1923). *Brain*, **46**, 73.
Ask-Upmark, E. (1944). *Acta. med. Scand.*, **116**, 502.
Biörck, G., and Nylin, G. (1944). *Nordisk. Med.*, **22**, 946.
Black, W. C., and Ravin, A. (1947). *Arch. Path.*, **44**. 176.
Broustet, P., and Berguignan, M., and L'Egrer, H. (1945). *Arch. Mal. Coeur.*, **38**, 212.
Carrillo, E. G., (1941). *Rev. Argent. Cardiol.*, **8**, 122.
Carrot, E., and David, M. (1943). *Rev. Neurol.*, **75**, 146.
d'Antona, L. (1935). *Minerva Med.*, **1**, 833.
Evans, W. (1944). *Brit. Heart J.*, **6**, 41.
Griffith, T. W. (1911–12). *Quart. J. Med.*, **5**, 229.
Guillain, G., and Rouques, L. (1932). *Ibid.*, **31**, 158.
Havier, P., and Decourt, J. (1933). *Rev. Neurol.*, **2**, 468.
Kolb, L. C., and Harvey, A. M., and Whitehill, M. R. (1938). *Bull., Johns Hopkins Hosp.*, **62**, 188.
Maas, O., and Zondek, H. (1920). *Z. Neur. Psych.*, **59**, 322.
Mondon, H., and Pasquet, D. (1939). *Arch. Mal. Coeur*, **32**, 401.
Röhrer, K. (1916). *Dtsch. Nervenheilk*, **55**, 242.
Segura, R. G., and Lanari, A. (1941). *Rev. Argent. Cardiol.*, **7**, 363.
Thaysen, E. H. (1943). *Ugeskr. Laeger.*, **105**, 329.
Thomasen, E. (1948). *Myotonia. Trans.*, by F. B. Carlsen, Aarhuus Stiftsbogtrykkerie A/S.
Waring, J. J., and Ravim, A., and Walker, C. E. Jr. (1940). *Arch. intern. Med.*, **65**, 763.

FURTHER EXPERIENCES WITH KHELLIN IN ANGINA OF EFFORT

BY

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In our previous paper (1950) the efficacy of khellin and of glyceryl trinitrate in preventing angina of effort and the electrocardiographic changes that may accompany it were compared in 12 susceptible patients. It was found that a single oral dose of 150 mg. khellin did have such an effect in a promising proportion of the patients but was less potent than a single 0·8 mg. (gr. 1/80) dose of glyceryl trinitrate. No ill-effects were produced by the khellin but no attempt was then made to give repeated treatment. Since then a number of papers have appeared on the subject of khellin. Best and Coe (1950) treated a group of nine patients with a daily oral dose of 150 mg. for from two to four weeks and found that the great majority had fewer attacks while under treatment and that it nearly always prevented pain when the patient was given an exercise, hypoxæmia, or ergonovine test. Nausea and vomiting occurred in only three of their patients but did not interfere with the use of the drug. Rosenman *et al.* (1950) treated a larger group of 30 patients with daily doses of 100–200 mg., Armbrust and Levine (1950) two groups of 28 and 25 patients with daily doses of 120 mg. or less, and Scott *et al.* (1951) a group of 20 patients with 17–240 mg. daily. Osher and Katz (1950) in a preliminary paper gave an account of their results with 19 patients, and Greiner and Gold (1950) in a brief summary their's with 39 patients. All these workers compared the frequency and severity of the anginal attacks while the patients were taking khellin with the results obtained with an inert control. Only Greiner and Gold failed to find any significant difference between the khellin and the control. Most of these papers, however, do also draw attention to the frequent toxic effects of the drug and acknowledge them as a serious drawback to its use. Fuller details of these and earlier papers are given in Table I, where so far as possible with data available, the results are compared with the series now reported, as well as with the original larger series described by Anrep *et al.* in 1949. The present investigation was undertaken in an attempt to reproduce Anrep's excellent results.

Method of Investigation

Preparation and Dosage of Drug. The preparation used was that recommended to us by Professor Anrep and used by him and by Ayad (1948) namely ammicardine, an extract made from the plant ammi visnaga by Alpha Laboratories of Cairo and marketed in tablets each of which is said to contain 50 mg. of khellin. The same preparation, ammicardine, was used in our previous tests (1950) but then in the form of a liquid extract. Dummy tablets were also used. Made of sucrose, they did not have the same appearance as the khellin, but the high incidence of side-effects that occurred with the khellin would in any case have prevented the patients from regarding the " genuine " and the dummy tablets as identical.

To begin with, a few patients were treated with the dose of khellin that Anrep *et al.* used, namely 100 mg. three times daily, but this proved so toxic that all subsequent cases were given an

initial dosage of 50 mg. three times daily after meals, and this was reduced, if toxic symptoms appeared, to the most that the patient could take. Sometimes this was as little as 50 mg. every other day. No facilities were available for estimation of khellin in the blood stream, but since it is known that the drug accumulates in the body such small doses are not necessarily inert.

Selection of Patients. Thirty-four patients with typical angina of effort were selected for this trial. Both sexes were accepted, accident determining that there were 9 women and 25 men. All cases seen were graded into mild, moderate, or severe. Mild cases were so called when they were able to lead an almost normal life, only developing angina on acts of exertion, unusually vigorous for them. They were called severe either when pain limited their walking distance on the level to 50 yards or less, or when pain appeared at rest. A few observations showed that mild cases were unsatisfactory for assessment since their pain was too infrequent and irregular. Accordingly this series of 34 includes only moderate and severe ones. Most of these suffered from pain at least once each day, and all had it several times a week. The only other patients rejected were those who proved unreliable witnesses, usually through confusing a co-existing benign left breast pain with their true angina of effort. All the patients were interviewed and examined by both of us. Standard and præcordial leads V I-6, and in special cases unipolar limb leads, were always taken before the investigation, and repeated after it, if there was reason to suspect a change. All appeared to be suffering from coronary atherosclerosis except Case 13 who had aortic stenosis. All except one severe case were tested as out-patients although a few of the more severe had to be brought to hospital by ambulance or car, and one could barely take a few steps from her chair.

Method. At the first interview the patient was asked to co-operate in a test to find out whether some new drug would prove helpful in his (or her) case. He was given a postcard on which to record at the end of each day for a week how many times he had had anginal pain, and whether his most usual precipitating factor (a set walk or climb, particular working conditions, the mid-day meal or, as in one patient, the act of defæcation) had in fact precipitated it. He was then given tablets and instructed to take one three times daily after food for a week and to keep a similar record during this period. He was told that should any unpleasant side-effects develop he was to cease taking the tablets for 24 hours and then to resume at two a day; if still upset he was to cease for a further 24 hours and then resume at one daily; if still upset he was to abandon treatment. When seen after this first test week his card was scrutinized and he was asked for his opinion as to how the tablets had influenced his pain, and any ill-effects were enquired about. If khellin had been given first, a week was allowed to elapse without treatment and then a second and similar trial begun with the dummies. If the dummies had been used first, the patient went straight on to khellin. Care was taken that the groups who began with khellin and those who began with dummies were of equal numbers and were strictly comparable as to age and sex. At the end of the second test period the same enquiries were made as after the first. In several instances it became necessary to carry on one or other trial period for more than one week, either because the original dose of khellin had caused severe side-effects and a dose which would be well tolerated, had to be found, or else because some change in the environment, e.g. a change in the weather interfering with a patient's habitual walk, a holiday from work, an intercurrent infection, or a period of shore leave in a seafaring man, had prevented the two trial periods remaining comparable.

At the end of the second trial period the value of the drug was assessed, partly by comparing the number of recorded attacks in the control, khellin, and dummy periods, partly on the basis of the patients' own opinion and our appraisal of the reliability of that opinion. Despite careful instruction patients were not very reliable in keeping records of their anginal attacks. Some attacks would be regarded as " too slight to be worth recording," others would be half forgotten so that only " several " would be put down. In other patients status anginosus would appear and to record it simply as one attack would be misleading. But by combining these records with the patients' expressed opinion, and by enquiring after and allowing for any variation in his environment and habits, it was not difficult for us to come to a confident conclusion as to the extent to which each patient's angina had really been alleviated.

Results

The four categories into which the 34 patients were placed and the number in each were as given below.

No Improvement	Slight Improvement	Moderate Improvement	No pain	Total
13	11	9	1	34

Where a patient recorded improvement with the dummy tablets, the degree of this—only once was it more than slight, and then the khellin had no beneficial effect—was subtracted from the result claimed for khellin. Full details of these results are given in Table II. Shortly, about one-third of the patients tested obtained worth while relief. It is perhaps of interest that the results were significantly better in the hypertensive (B.P. more than 160/90) than in the others.

TABLE I

Summary of Clinical Trials with Khellin

Authors	No. of cases	Daily dose in mg.	Response to Treatment			Toxic Effects		
			Satisfactory	Doubtful	Failure	Mild or Moderate	Severe	Total
Ayad (1948) ..	23	100–200	83%		17%	0	0	0
Anrep *et al.* .. (1949)	250	c. 120–150 50–100	90%		10%	A few	None	A few
Rosenman *et al.* (1950)	30	100–200	40%	53%	7%	20%	33%	53%
Armbrust Gp. I	28	120 Later 40–80	28·5%	28·5%	43%	43%	25%	68%
and Levine Gp. II	25		52%		48%	56%		56%
Best and Coe .. (1950)	9	150	78%	11%	11%	33%	0	33%
Greiner and Gold (1950) ..	39	100–150			100%			?
Osher and Katz (1950)	19	120+	84% 79%	5%	16%	Several	10%	?
Scott *et al.* .. (1950)	20	17–240 Av 106	20%	35%	45%			85%
Present Series ..	34	150 Later 25–150	29%	32%	38%	76%	21%	97%

Toxic Effects. The high incidence of these is shown in Tables I and II. On a dosage of 150 mg. daily, their incidence was:—

None	Slight	Moderate	Severe	Total
1	8	18	7	34

Gastric upset, comprising dyspepsia, nausea, or heartburn, occurred in 33 of the 34 patients and in 11 led to vomiting. Giddiness was complained of six times, lassitude and headache three times, and two patients developed a mild desquamating dermatitis. In many instances the gastric symptoms began soon after the first tablet had been swallowed, presumably owing to a local effect upon the stomach, but more often the onset was delayed until after several tablets had been taken. Since the drug accumulates in the body, it is probable that in these patients the blood concentration had risen to a toxic level.

TABLE II

Case	Sex	Age	Angina: Duration and Severity	Blood Pressure	Tolerated Dosage (mg. per day)	Toxic Effects	Degrees of Improvement	Remarks
1	M	60	4 yr. +++	190/115	300	+	0	
2	M	59	2 yr. ++	110/90	<300	+++	0	Refused treatment after 3 days.
3	F	54	3 yr. +++	250/140	50	++	+	
4	F	56	2 yr. +++	160/100	≤150	++	0	
5	M	50	1 yr. +++	140/95	≤150	+++	+	Developed skin rash.
6	M	60	5 yr. ++	170/120	100	++	+	
7	M	62	1 yr. ++	115/80	100	++	+++	Skin rash on 150 mg. daily.
8	F	57	3 yr. +++	145/70	≤150	+++	0	Diabetic. Died during treatment.
9	F	56	Several yrs. ++	230/110	150	+	+	Diabetic.
10	F	66	18 mo. +++	150/100	50	++	0	
11	F	65	2 yr. ++	250/120	150	+	+	
12	F	62	4 yr. +++	220/140	100	++	+	
13	M	63	9 mo. ++	150/120	150	+	+	Aortic stenosis
14	M	46	2 yr. +++	150/90	100	++	0	
15	M	44	3 mo. ++	125/95	150	+	++	
16	M	55	5 mo. ++	130/80	150	+	++	
17	M	45	3 mo. ++	140/80	≤150	+++	0	Fainted, treatment stopped.
18	M	57	15 mo. ++	130/80	50	++	++	
19	M	48	9 mo. +++	105/60	< 50	+++	0	
20	M	47	2 yr. ++	150/100	50	++	0	
21	M	55	3 yr. +++	170/105	150	0	++	
22	M	46	2 mo. ++	190/110	100	++	++	Small cardiac infarct during treatment.
23	M	63	7 mo. ++	160/90	50	++	++	
24	M	50	9 mo. ++	110/70	< 50	+++	0	Had a duodenal ulcer.
25	M	51	2 yr. ++	150/95	100	++	++	
26	F	67	2 yr. ++	170/105	≤100	+++	0	
27	M	63	3 mo. +++	230/110	150	+	+	
28	F	50	9 mo. ++	200/100	25	++	+	
29	M	63	1 yr. +++	140/90	150	+	++	
30	M	45	11 mo. ++	145/105	100	++	0	
31	M	49	4 mo. ++	125/70	25	++	0	
32	M	49	16 mo. ++	130/90	75	++	++	
33	M	43	3 yr. ++	210/150	50	++	+	
34	M	63	7 yr. ++	210/110	50	++	+	

Severity of Angina: ++=moderate, +++=severe.
Toxic Effects of Khellin: +++=sufficient to cause treatment to be abandoned, +=not sufficient to cause reduction of dose below 150 mg. daily.
Degree of Improvement: +=slight, ++=moderate, +++=no pain.

SUMMARY

Thirty-four patients with moderate or severe angina of effort were treated with khellin, beginning with doses of 150 mg. daily, and the effect of the drug assessed against dummy controls.

Ten patients (29%) were moderately or greatly improved and 13 (38%) were total failures.

There was a high incidence of toxic effects on this dosage, and seven patients had to abandon treatment.

The drug has a limited place in the treatment of angina of effort.

Our results with this drug agree well with those of Armbrust and Levine and also with those of Scott *et al.* (Table I). Our incidence of toxic effects is higher, presumably because the 150 mg. daily dose was persevered with for longer. Possibly with more careful attention to dosage a few

patients who were failures might have obtained useful relief, but it is very doubtful whether the proportion of worthwhile results with this substance in moderate or severe angina can be raised above 40 per cent. We agree with these workers that the toxic effects of khellin constitute an important drawback to its use.

We wish to express our thanks to colleagues who have referred cases to us, and especially to Dr. W. G. A. Swan of the Newcastle General Hospital. We are also grateful to the Governors of the Royal Victoria Infirmary for a grant towards expenses.

REFERENCES

Ayad, H. (1948). *Lancet*, **1**, 305.
Anrep, G. V., Kenawy, M. R., and Barsoum, G. S. (1949). *Amer. Heart J.*, **37**, 531.
Armbrust, and Levine, S. A. (1950). *Amer. J. med. Sci.*, **220**, 127.
Best M. M., and Coe, W. S. (1950). *Circulation*, **2**, 344.
Dewar, H. A., and Grimson, T. A. (1950). *Brit. Heart J.*, **12**, 54.
Greiner, T., and Gold, H. (1950). *J. Pharmacol. and Exper. Therap.*, **98**, 10.
Osher, H. L., and Katz, K. H. (1950). *Boston M. Quart.*, **1**, 11.
Rosenman, R. H., Fishman, A. P., Kaplan, S. R., Levin, H. G., and Katz, L. N. (1950). *J. Amer. med. Assoc.*, **143**, 160.
Scott, R. C., Iglauer, A., Green, R. S., Kaufman, J. W., Berman, B., and McGuire, J. (1951). *Circulation*, **3**, 80.

HYPERTONIC SALT SOLUTION INTRAVENOUSLY AS A TEST FOR CORONARY DISEASE

BY

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Among the patients, who consult the heart clinic, there are some who can be diagnosed only by clinical means. In patients who present some vague præcordial and thoracic complaints of anginal character, we thought it would be advantageous to add to our diagnostic methods a new test that would give us an objective sign of angina pectoris.

The anoxæmia and exercise tests are already used successfully. The method we have used was proposed by Scherf and Weisberg, and repeated by Lequime and Denolin in 1945, but does not seem to be in prevalent use. We repeated the observations of Lequime and Denolin in cases from our outpatient department who presented with anginal pains.

The patients chosen presented with angina; however the clinical, fluoroscopic, and electrocardiographic examinations were normal, not giving any objective signs of angina, except that two of them showed slight modifications of the T waves.

After completion of the above routine examinations, we injected rapidly in the antecubital vein of one or the other arm 40 ml. of a 20 per cent solution of sodium chloride. We noted the physical reactions of the patients during and some minutes after the injection. In order to give time for the development of any electrocardiographic modifications, we repeated the cardiogram eight minutes after the injection of the hypertonic salt solution, using the three standard leads and the unipolar limb and præcordial leads. We compared then the cardiogram taken after the injection of the hypertonic solution with that taken before the injection, and noted any resultant modifications.

We studied twenty patients, ten men and ten women. The patients were aged between 32 and 69 years. The most frequent symptom noted was substernal, præcordial, or thoracic pain, with or without radiation to the shoulders, the arms, and the neck. The pain appeared characteristically after exercise, but occasionally in the resting position. Many patients complained of shortness of breath after exercise. Other less frequent symptoms were palpitation, headache, dizziness, oppression, and weakness.

Examination of the lungs was normal by physical means. The heart was either normal or presented some auscultatory sign such as an apical systolic murmur, a split second sound, a snapping second sound, distant heart sounds, or tachycardia. The blood pressure was normal in the majority of the cases; 8 of the 20 patients had increased pressures. The systolic pressure of the 20 patients ranged between 120 mm. and 230 mm., the diastolic pressure between 70 mm. and 130 mm. In three cases the heart was slightly enlarged on fluoroscopy; in one the hilar markings were increased; in another the apex was slightly immobile.

During the injection of the hypertonic solution the majority of the cases presented a sensation of warmth on the face and head; occasionally they experienced a sensation of warmth in different locations of the body, or at other times a burning sensation in the throat, pain in the left shoulder, headache, nervousness, drowsiness, or torpor.

Before the injection, the electrocardiogram was normal in 18 cases. In the remaining two we observed a slightly negative T wave in leads I and II, in VL, and in V4, V5 and V6.

In the great majority of the cases the electrocardiogram did not show any modification after the intravenous injection of the hypertonic salt solution.

In one-third of the cases we noted some insignificant modifications, which did not permit the diagnosis of angina pectoris. In only one case did we find a characteristic change: an elevation of 2 mm. of the S–T segment in V1 and V2 and a depression of 2 mm. of the S–T segment in leads V4 and V5.

In half of the cases the diagnosis of angina pectoris was made clinically. The rest of the cases were diagnosed as intercostal or thoracic pains or as pain of psychosomatic nature.

Summary and Conclusions

The test using an intravenous injection of a hypertonic salt solution was done on twenty patients who presented with pain in the chest. In eighteen the electrocardiogram was normal before the injection of the hypertonic solution. In the other two there was a negative T wave in leads I, II, VL, and V4, V5, and V6.

An intravenous injection of 40 ml. of a 20 per cent sodium chloride solution was given and a second electrocardiogram was taken eight minutes after injection. In two-thirds of the cases, the electrocardiogram taken after the injection of the hypertonic solution showed no modification in relation to the tracing taken before injection. In the remaining third, insignificant modifications were noted, which were not considered of clinical importance; thus it was not possible to diagnose angina pectoris from these changes alone. In only one case following the injection of hypertonic salt solution did a significant change of the S–T segment occur.

In conclusion, the intravenous injection of hypertonic salt solution does not, in the great majority of the cases, give rise to significant modifications of the electrocardiogram. The use of this test can not replace the exercise or the anoxæmia tests in the diagnosis of angina pectoris, which have been shown to be of value in other series of similar cases.

References

Borst, J. R., and Holleman, E. J. (1947). *Nederl. Tijdschr. Geneesk*, **41**, 2905.
——, —— (1948). *Acta med. Scand.*, **130**, 26.
Lequime, J., and Denolin, H. (1945). *Arch. Mal. Coeur.*, **38**, 231.
Onozaki, N. (1925). *Tohuku J. exp. Med.*, **24**, 580.
Silbert, J. (1930). *J. Amer. med. Ass.*, **94**, 1730.
Walcott, W. W., and Deyrup, I. J. (1948). *Amer. J. Physiol.*, **154**, 328.

CALCIFICATION OF THE AORTIC VALVE AND OF THE CORONARY ARTERIES

BY

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This paper reports a clinical and radiological survey to find the frequency of calcareous aortic stenosis and of calcification elsewhere in the heart. 400 men over the age of 60 were chosen at random—200 in- or out-patients of a general hospital (series A) and 200 in-patients of a mental hospital (series B). In the clinical examination Levine's (1945) method of grading the loudness of murmurs was used. The technique of X-ray screening was that described by Sosman (1943). To compare the clinical and post-mortem incidence of cardiac calcification, 72 hearts from consecutive routine necropsies were radiographed.

RESULTS

Among the 400 men, 27 cases (6·75%) of cardiac calcification were detected on screening: aortic valve (Fig. 1), 11 cases (2·75%); coronary arteries (Fig. 2, 3 and 4), 14 cases (3·5%); mitral valve (Fig. 5), 1 case; pericardium, 1 case.

Calcified aortic valve. The clinical findings in these 11 cases are set out in Table I, and their average age, compared with other patients', in Table II. There was no past history of rheumatic fever. Six of the seven men in series A had been passed fit for military service in 1914–18 and three had served throughout that war. Three of the four men in series B, being examined annually, were noted, after being found free of murmurs for 12, 31 and 37 years, to have developed systolic murmurs at the ages of 65, 54 and 66 respectively. In only three patients was dyspnœa a feature; one patient had a history of six months' angina of effort.

The physical signs were those generally found in aortic stenosis. The second heart sound at the base was diminished or absent in all cases except one. A systolic murmur was present in all and a diastolic in one; there was a systolic thrill in five patients. However, none had a plateau pulse and, in all except one, the pulse pressure was normal. Electrocardiograms were taken in six cases. Three showed left ventricular preponderance, one auricular fibrillation with incomplete right bundle branch block, one left axis deviation, and one was normal.

On screening, the left ventricle was enlarged in 7 cases. Calcification, when present, was always seen in the right anterior oblique position (Fig. 1.) but in the left anterior oblique in only seven cases. There was no clinical or radiological evidence of mitral stenosis in any case.

Two patients have died, both of them suddenly.

Calcified coronary arteries were detected, by screening, in 14 cases (Fig. 2, 3, and 4). They were significantly older than the patients without coronary calcification (see Table II). The clinical histories showed nothing significant except for a patient with effort dyspnœa whose blood pressure was 270/160. There was hypertension in four patients (diastolic over 100). There was a systolic murmur in seven, of whom three were hypertensive.

Calcification was seen in the left coronary artery in 10 cases (circumflex 9, descending 1), in the

FIG. 1.—Calcified aortic valve—R.A.O. view.

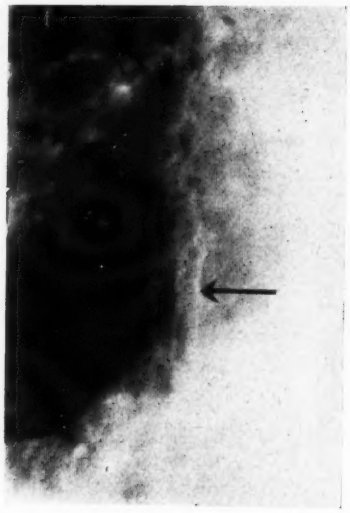

FIG. 2.—Calcified right coronary artery. Patient slightly rotated to his right, i.e. a 5° left anterior oblique view.

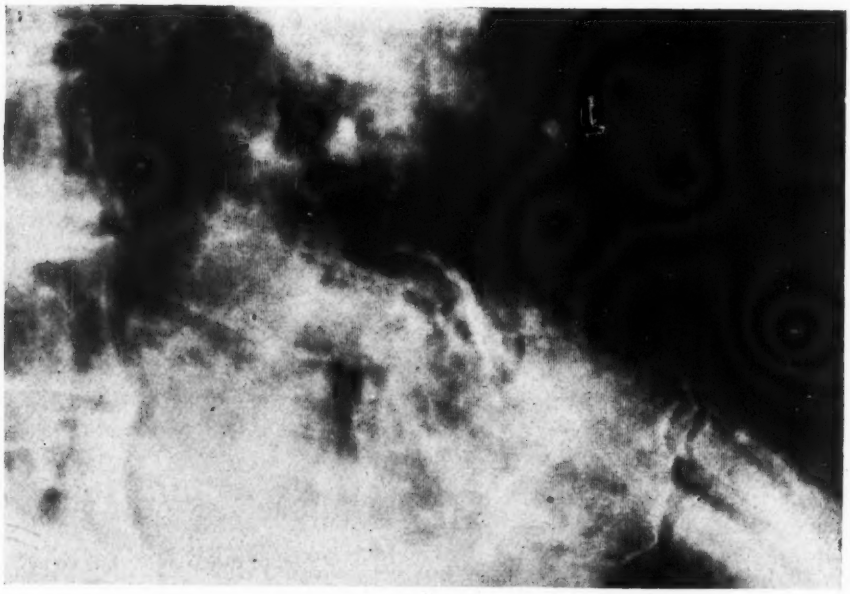

FIG. 3.—Calcified left coronary artery (descending branch). In this view (R.A.O.) the positions of the descending and circumflex branches are similar.

TABLE I

CLINICAL AND RADIOLOGICAL FINDINGS IN ELEVEN CASES OF CALCAREOUS AORTIC STENOSIS

	Case No.	Age	Past history and Military Service	Dyspnœa	B.P.	Heart Sounds				Murmurs *				Basal Systolic Thrill	Screening. Valves seen in		Enlargement of L.V.
						Apex		Base		Apex		Base					
						1st	2nd	1st	2nd	S.M.	D.M.	S.M.	D.M.		R.A.O.	L.A.O.	
Series A	1	67	Nil	0	160/90	n	–	n	–	4	0	4	0	+	+	+	++
	2	68	Army 1914–18	0	150/90	n	–	–	–	4	0	4	0	0	+	+	n
	3†	74	Police 1897–1922	+	150/80§	–	–	0	–	3	0	4	0	+	+	0	++
	4†	62	Territorials 1910	0	155/70	–	–	–	–	3	0	3	0	0	+	+	n
	5	82	Passed fit 1914, exempted	slight	110/70	–	–	–	–	1	0	2	0	0	+	+	+
	6	84	Passed fit aged 20	0	140/90	n	–	n	–	2	0	4	0	+	+	+	+
	7	70	Army 1900 and 1914–18	+	135/85	n	n	n	0	3	0	3	0	0	+	0	++
	8	76	Army 1914–18 Heart normal 1927–38. SM 1939	0?	160/100	n	–	0	0	3	0	5	0	+	+	+	n
Series B	9	63	Heart normal 1910–40. SM 1941	0?	160/95	n	n	–	n	2	0	3	0	0	+	0	n
	10	68	SM 1943, on admission	0?	165/145	n	–	n	0	3	0	4	0	?	+	0	++
	11	74	Heart normal 1905–41. Murmur 1942	0?	150/100	n	n	n	–	3	early	3	0	+	+	+	+

n=normal, –=decreased, 0=absent. SM=Systolic murmur, DM=Diastolic murmur. †Died. Necropsy in Case 3 showed coronary artery as well as aortic valve calcification. *Levine's (1945) grading is used. §Auricular fibrillation.

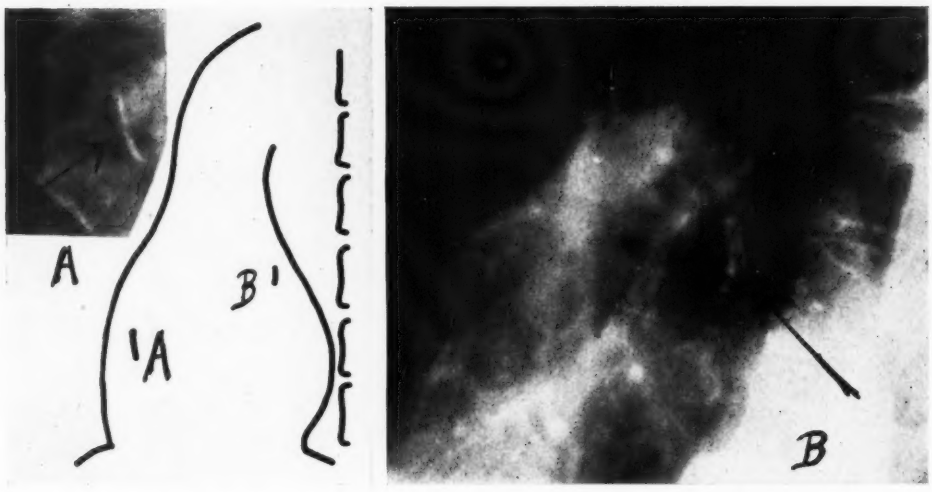

FIG. 4.—Calcified left coronary artery. Two pictures illustrate the distinction between the descending and the circumflex branches in the left anterior oblique view. The descending branch is seen near the anterior border of the heart (A) and the circumflex branch near the posterior border (B).

right coronary in 3, and in the right and circumflex branch of the left in one case. There was no cardiac enlargement except in the presence of hypertension.

Electrocardiograms were taken in three of the four cases in series A. One showed left ventricular preponderance and the other two were normal. The Wassermann reaction was done in eight cases and was negative.

Calcification of the mitral valve was detected in one man and was confirmed at necropsy. Calcification of the pericardium was found in one man who gave no past history of rheumatic or tuberculous disease and who had neither symptoms nor signs of heart disease.

No case of calcification confined to the annulus fibrosus nor of the myocardium was observed.

RADIOGRAPHY OF THE ISOLATED HEART POST MORTEM

72 hearts of patients of all ages (of whom 50 were over 60) from consecutive routine necropsies were radiographed. In this way small areas of calcification can be seen—areas that are too slight to be detected by X-ray screening during life or even by naked-eye examination at necropsy. Figures based on post-mortem radiography showed an incidence of calcification in the aortic valve in patients over the age of sixty of 44 per cent (22 out of 50), whereas in a series of 563 necropsies

TABLE II

AVERAGE AGE OF DIFFERENT GROUPS

	Series A		Series B		All cases	
	Number	Age	Number	Age	Number	Age
With calcified aortic valves ..	7	72·4	4	70·3	11	71·6
With calcified coronary arteries ..	4	72	10	74	14	73·4
Without cardiac calcification ..	187*	68·1	186	68·4	373*	68·3

* Excluding one case of pericardial and one of mitral valve calcification.

FIG. 5.—Calcification of the mitral valve. Right anterior oblique position. The appearance is distinct from that of the aortic valve (Fig. 1), the calcification being compact and nodular in the mitral, but fragmented and irregular in the aortic valve.

naked-eye examination gave a figure of only 5·5 per cent for the same age group. This suggests that post-mortem radiography reveals calcification eight times as often as naked-eye examination.

The findings in the 72 hearts are set out in Table III. In 22 hearts (30%) there was calcification of the aortic valve. Usually this consisted of one or two small flecks of calcium along the line of attachment of the valve cusps, but it often extended into the leaflet and in three cases was only present in the leaflet (Fig. 6). The calcification tended to spread inwards from points on the ring

TABLE III

RADIOGRAPHY OF THE HEART POST MORTEM

	Number of cases	Percentage of whole series	Average age
Whole series	72	100	65
With calcification in aortic valves	22	30	75
Without calcification in aortic valves	50	70	61
With calcification in coronary arteries	38	53	70
Without calcification in coronary arteries	34	47	61

at 4 o'clock and 8 o'clock. In no case was there any narrowing of the valve orifice. All but four of the cases also showed coronary artery calcification.

Four of the 22 cases had been noted to have systolic murmurs. In sixteen no murmurs had been recorded and in two there were no notes. All 22 were over 60 and their average age was 14 years more than that of the remainder.

Calcification of the coronary arteries was present in 38 cases (53%) and was commoner in the left than in the right. Those with coronary artery calcification were, on the average, nine years older than those without it. Sixteen of eighteen patients over the age of 75 had calcification of the coronary arteries and 14 also of the aortic valve.

Mitral valve calcification was present in the hearts of four women, but in only one was there stenosis. Two of the others were noted to have had systolic murmurs; the findings in the third were not recorded.

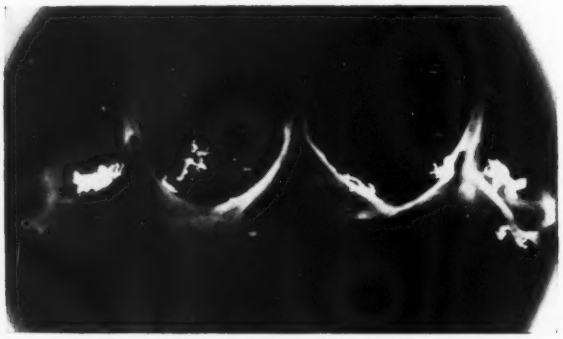

FIG. 6.—Typical calcification in the aortic valve of a man aged 81. The calcium is situated along the line of attachment of the cusps and in the leaflets. This man, who had not been screened in life, presented no sign of heart disease.

FIG. 7.—The aortic valve of a man aged 72 with Lutembacher's syndrome. When he was screened during life no calcium was detected. Presumably more calcium than this must be deposited before it can be seen on the X-ray screen.

DISCUSSION

Cardiac calcification is more easily detected by fluoroscopic screening than by radiography. When taking radiographs, as when screening, it is best to use a small aperture.

Calcareous aortic stenosis. McGinn and White (1934) found aortic stenosis in 2·3 per cent of 4800 cardiac patients, but do not separate those with calcification. Habbe and Wright (1939) detected valvular calcification in approximately 1·5 per cent of 1000 patients over the age of 40 "referred for cardiac roentgen study," but they do not state how many were aortic. The incidence of calcareous aortic stenosis at necropsy was found by Friedewald and Ewing (1938) to be 0·3 per cent, and by McGinn and White (1934) to be 1·8 per cent.

The clinical picture of aortic stenosis in these eleven cases conforms to that described by McGinn and White (1934) and by Contratto and Levine (1937). Only three presented with breathlessness or pain on effort and the others would presumably not have been diagnosed as suffering from aortic stenosis unless they developed symptoms of heart trouble.

Since only half the patients had thrills and only one had a reduced pulse pressure, the diagnosis was not always certain before screening. The presence of calcification in the aortic valve establishes the diagnosis of aortic stenosis (Wood, 1948). Whether aortic stenosis ever occurs in this age group without calcification is doubtful. There is no recent report of aortic stenosis in a patient of 60 without calcification also being noted (Davies and Steiner, 1949; McGinn and White, 1934; Contratto and Levine, 1937; Gibbs, 1935; Dry and Willius, 1939; Kumpe and Bean, 1948; and Lewes, 1951): however, not all the patients described by these authors were screened during life, the calcification being discovered at necropsy; nor were all their ages recorded.

FIG. 8.—Calcareous aortic stenosis (Case 4). Calcification of the valve was seen on fluoroscopic screening during life.

Previous reports on necropsy material mention the infrequency with which a correct diagnosis has been made during life (a third in the series of McGinn and White's (1934) and a half in that of Thompson and Levine's (1936)). If the presence of a persistent systolic murmur in an elderly person is taken as an indication for screening, the diagnosis of aortic stenosis should be made with a high degree of accuracy.

The amount of calcium that must be present in the aortic valve to be visible on the screen presumably varies with the build of each patient. But Fig. 7 shows the aortic valve of a man of 72, not in this series, who had Lutembacher's syndrome. Screening during life did not reveal the valvular calcification. Calcification in Case 4, on the other hand, had been easily detected on screening and at necropsy was found to be extensive (Fig. 8). The amount of calcium that must be present to be visible on screening in life may lie between these two extremes.

There are two opposing views on the ætiology of calcareous aortic stenosis. Karsner and Koletsky (1947) have summarized the evidence in support of a rheumatic basis and in their own series of 200 necropsy cases they found histological evidence of past rheumatic infection of the heart in 98 per cent. The theory that the condition may often be atheromatous, originally put forward by Mönckeberg in 1904, is supported by pathologists who have not found such frequent histological evidence of past rheumatism (Sohval and Gross, 1936; Friedewald and Ewing, 1938; and Hultgren, 1949). The rheumatic theory is the more widely accepted by clinicians (Parkinson, 1949; Dry and Willius, 1939; McGinn and White, 1934; Contratto and Levine, 1937). There does not seem, however, to be agreement on the definition of histological evidence of past rheumatic infection of

the heart. The figures for the incidence of such evidence in unselected material vary from 11 per cent (Hultgren, 1948) to 93 per cent (Hall and Anderson, 1943).

Three of the four patients in series B with aortic stenosis were known not to have developed murmurs until the ages of 65, 54, and 66. This late development of the murmur suggests that, if these patients had had rheumatic fever, there had either been an exceptionally long interval between it and the development of the murmur or the rheumatism had occurred later in life than is usual.

The average age of the eleven cases of aortic stenosis was higher than the average for the rest (excluding other cases of cardiac calcification) but the difference was not statistically significant ($t=1{\cdot}689$, $P=0{\cdot}092$). Sophian's (1945) series also shows an age difference: he reported 31 cases of calcareous aortic valvular stenosis from 500 necropsies, whose average age was 49, and divided them into 17 rheumatic and 14 non-rheumatic, chiefly on the basis of involvement of the mitral valve. From his figures one can calculate that the average age of the rheumatic group was 46; of the non-rheumatic group it was 60. In Ashworth's (1946) series of 500 necropsies, the patients with calcareous aortic stenosis were considerably older than the rest. It seems unlikely that any group of patients with rheumatic heart disease lives for longer than normal people.

Hultgren (1948) radiographed 100 hearts from routine necropsies and found calcium in the aortic valve in 46. Windholz and Grayson (1947) quote 8 per cent as the necropsy incidence of valvular calcifications. In this series aortic valve calcification was found in 22 hearts out of 72. The fact that these patients are older than the rest suggests that the calcification of the aortic valve, as detected by post-mortem radiography, is a degenerative condition. The pattern of valve calcification appeared to be similar in the 22 shown at necropsy and in the 2 diagnosed in life as suffering from calcareous aortic stenosis (Fig. 6 and 8). The pattern of calcification in the aortic valve, where it is fragmented and irregular, is distinct from that in the mitral where the calcium is compact and nodular (Cf. Fig. 1 and 5).

Coronary artery calcification. This was found by Habbe and Wright (1950) in approximately 3 per cent of their 1000 patients over 40 years of age. Sosman in 1943 reported coronary artery calcification in 42 of 204 cases of cardiac calcification that he had then seen.

When a calcified left coronary artery is seen on the screen it may be impossible to distinguish between the descending and the circumflex branches in the first oblique view, but in the second oblique the circumflex is seen near the posterior border of the heart and the descending near the anterior border (Fig. 3 and 4). The movement of the coronary arteries is usually marked, especially near their origin from the aorta. Coronary vessels may be distinguished from aortic valves, not only by their position and movement, but because they are usually linear and nearly homogenous shadows, whereas calcified aortic valves appear irregular and granular (Fig. 1). Since post-mortem radiography shows that about half of all hearts show coronary artery calcification it is clear that only a fraction of these cases are diagnosed in life.

Patients in this series with coronary artery calcification did not show clinical evidence of impaired coronary function.

Summary and Conclusions

400 men over the age of sixty were examined clinically and radiologically in order to determine the incidence of cardiac calcification.

Calcification of the aortic valve was found in eleven (2·75%) and of the coronary arteries in fourteen (3·5%).

The patients with calcification of the aortic valve presented the signs of aortic stenosis. Their average age was slightly greater than that of the patients without calcification. Three men with calcareous aortic stenosis were known not to have developed murmurs until the ages of 65, 54, and 66.

Radiography of the isolated heart post-mortem showed calcium in the aortic valve in 2[illegible] of

72 cases. These patients were 14 years older, on an average, than those without aortic valve calcification. It is suggested that calcareous aortic stenosis may be a degenerative disease.

Coronary artery calcification was not associated with evidence of impaired coronary function. By post-mortem radiography it was found to occur in 38 of the 72 cases. Patients with coronary artery calcification were, on an average, older than those without it.

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REFERENCES

Ashworth, C. T. (1946). *Arch. Path.*, **42**, 285.
Contratto, A. W., and Levine, S. A. (1937). *Ann. intern. Med.*, **16**, 1636.
Davies, C. E., and Steiner, R. E. (1949). *Brit. Heart J.*, **11**, 126.
Dry, T. J., and Willius, F. A. (1939). *Amer. Heart J.*, **17**, 138.
Friedewald, W. F., and Ewing, A. R. (1938). *Amer. J. med. Sci.*, **196**, 400.
Gibbs, A. J. (1935). *Guy's Hosp. Rep.*, **85**, 275.
Habbe, J. E., and Wright, H. H. (1950). *Amer. J. Roentgen.*, **63**, 50.
Hall, E. M., and Anderson, L. R. (1943). *Amer. Heart J.*, **25**, 64.
Hultgren, H. N. (1948). *Arch. Path.*, **45**, 694.
Karsner, H. T., and Koletsky, S. (1947). *Calcific Disease of the Aortic Valve*, Philadelphia.
Kumpe, C. W., and Bean, W. B. (1948). *Medicine*, **27**, 139.
Levine, S. A. (1945). *Clinical Heart Disease*, Philadelphia.
Lewes, D. S. (1951). *Brit. med. J.*, **1**, 211.
McGinn, S., and White, P. D. (1934). *Amer. J. med. Sci.*, **188**, 1.
Monckeberg, J. G. (1904). *Virchows Arch.*, **146**, 472.
Parkinson, J. (1949). *Lancet*, **1**, 895.
Sohval, A. R., and Gross, L. (1936). *Arch. Path.*, **22**, 477.
Sophian, L. H. (1945). *Amer. J. med. Sci.*, **210**, 644.
Sosman, M. C. (1943). *Amer. J. Roentgen.*, **50**, 461.
Thompson, W. P., and Levine, S. A. (1936). *New. Engl. J. Med.*, **215**, 670.
Windholz, F., and Grayson, C. (1947). *Amer. J. Roentgen.*, **58**, 411.
Wood, P. (1948). In *Modern Trends in Diagnostic Radiology* (Ed. McLaren), London.

DISSECTING ANEURYSM OF THE AORTA IN MOTHER AND CHILD

BY

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Shennan's report on dissecting aneurysm of the aorta (1934) was based on 297 cases. Ten years later Schnitker and Bayer found that the total number of cases had risen to 580; of these, 141 (24%) occurred before the age of 40 and these form the subject of their paper. Of the total 141, 92 were males and 49 females; in 24 of the females (49%) the aneurysm occurred in association with pregnancy. Another point of interest emerging from this study is the occasional occurrence of dissecting aneurysms in childhood and adolescence: 31 cases—5 per cent of the total 580—occurred in the age range 1 to 20 years.

In this paper we report a further case associated with pregnancy and a case in a 14-year-old boy. The patients were mother and son and this fact adds special interest. It may be no more than coincidence that two such close relatives should die of the same uncommon disease; it suggests, however, the possibility of a hereditary predisposition to dissecting aneurysm and the need of investigating the family history in this disease.

Case 1

The patient, aged 34, had always been regarded as delicate; she easily became tired and exhausted and found hills a great effort. She used to suffer from low backache, but never seems to have complained of pain in the mid-thoracic region. There were no other illnesses of note. She bore four children: the first was our Case 2; the second and third are alive and well; the fourth was one month premature and lived for only two weeks; the cause of death of this child is not known.

She did not get up after this last confinement, and on the sixth day she suddenly felt she was "sinking through the bed"; she did not complain of pain or any other symptoms. On the seventh day she experienced the same feeling, but on the eighth day she felt very much better and remained so for some 36 hours. On the ninth day she "felt herself going," became progressively more and more dyspnœic, and died.

At *necropsy* the body was thin and sallow; there were no external injuries. The heart showed fatty infiltration; the coronary arteries were patent. The aorta showed patches of atheroma, but the main lesion was a dissecting aneurysm involving the first three inches of the abdominal aorta. The abdominal cavity was full of blood clot. The liver and spleen were pale and friable, the stomach and intestines normal. The uterus showed normal involution and there was no sign of uterine infection. The brain was not examined. The anatomical diagnosis was ruptured dissecting aneurysm of the abdominal aorta and atheroma of the aorta. No tissue was taken for histological examination.

Case 2

This patient, the first child of the previous patient (Case 1) was 14 years old. There had been no difficulty in the confinement or puerperium and he was normally developed at birth. He was an able child and had won a scholarship at the age of 12. He found physical exertion exhausting and did not take part in the usual school games; he ran as little as possible. At the age of 11 he had an attack of pleurisy, and a few months before his death he had an upper respiratory infection, which kept him in bed for a week.

At 6 p.m. on the day of his death, he was playing boisterously with his sister and in the process knocked his head on the wall; he did not complain unduly of this. At 10 p.m. he was playing with his brothers and sisters before going to bed. At 10.15 p.m. he sat down on the settee to take off his shoes; he had removed one and was in the act of removing the other when he complained of a sudden sharp pain in the chest. He immediately ran upstairs to his sister, who went for help at once. He then came downstairs and stood at the front door. He spat up a quantity of blood and became very frightened; he lay down on the settee and began to become faint.

On examination a few minutes later, he was almost pulseless, cold, pale, and sweating profusely. He was semi-comatose and in such obvious agony that it was impossible to examine him satisfactorily. Spontaneous pneumothorax was suspected; the boy was carried upstairs to his bed to await an ambulance, but he died before it arrived. When the body was removed after death it was obvious from the splash that the thorax was full of fluid.

At *necropsy* the skull was found to be healthy; the meninges were pale from loss of blood. The pericardium and heart were healthy and the cavities of the heart contracted. Both lungs were collapsed and the mediastinum contained an irregular hæmorrhagic mass about 13 cm. in diameter which showed on its left side a rupture about 4 cm. long. Blood had tracked downwards on the posterior mediastinum and clots were found behind the peritoneum. There was some free fluid in the lesser sac. The liver was pale, the spleen contracted and, on section, like soft putty. The other viscera were normal. The thoracic viscera were sent to the laboratory for further study.

The *specimen* was a blood-sodden mass consisting of the larynx, trachea, bronchi, and parts of the left lung and aorta. The aortic segment included most of the arch; when opened longitudinally it showed no lesion; when cut transversely it showed a dissecting aneurysm in the media extending over about two-thirds of the circumference of the aorta. The upper limit of the dissection could not be located with certainty and the lower limit was not included in the specimen.

For *histological examination*, pieces of dissected and non-dissected aorta were fixed in 10 per cent formol-saline and sectioned transversely. The stains applied are shown in the accompanying table. Paraffin sections were used except for sudan IV, which required frozen sections. All the sections were examined under a polarizing microscope, as well as in the ordinary way.

STAINS APPLIED TO AORTA AND REACTION OF MUCOID MATERIAL IN MEDIA

Stain	Reaction	Stain	Reaction
Gomori for reticulin	Negative	Mucicarmine	Negative
Hæmalum	Bluish	Sudan IV and hæmalum ..	Negative for fat
Hæmalum and eosin	Bluish	Prussian blue for free iron ..	Negative
Hale's iron (1946)	Green	Toluidin blue	Reddish-purple
Heidenhain's azan	Uncertain	Van Gieson	Uncertain
Kossa for calcium	Negative	Van Gieson and Weigert's elastin	Negative for elastin
McManus (1948) for Schiff reaction	Pink	Weigert's elastin	Negative
Methyl violet for amyloid ..	Negative	Weigert's iron hæmatoxylin and eosin	Bluish

At the edges of the aneurysm, the split was at the junction of the outer third and inner two-thirds of the media (Fig. 1). The outer wall of the aneurysm tapered rapidly from the edges and most of it was extremely thin. Further splitting of the outer wall had occurred near one edge (Fig. 2). The aneurysm was lined by a thick irregular layer of blood clot showing no evidence of organization. The adventitia was obscured by hæmorrhage but the intima was normal. The composition of the media was the same in both the dissected and non-dissected pieces of aorta. Elastic tissue, reticular fibrous tissue (Fig. 3) and muscle were present, but the laminæ of these tissues were separated by mucoid material, which was most abundant in the inner half of the media (Fig. 4).

This mucoid material did not have the histological appearance of necrotic muscle or necrotic collagen. It was a homogeneous, afibrillar substance showing no birefringence with polarized light. It contained moderate numbers of small cysts or bubbles; these may well have been artefacts indicating its friable nature, since they were especially numerous along scratches produced accidentally during preparation of the sections.

FIG. 1.—*Case* 2. Transverse section of aneurysm showing its very thin outer wall. The interruption in this wall (top of figure) and that in the unsplit part of the aorta (bottom of figure) represent incisions made for inspection. Weigert's elastin stain. (× 4½.)

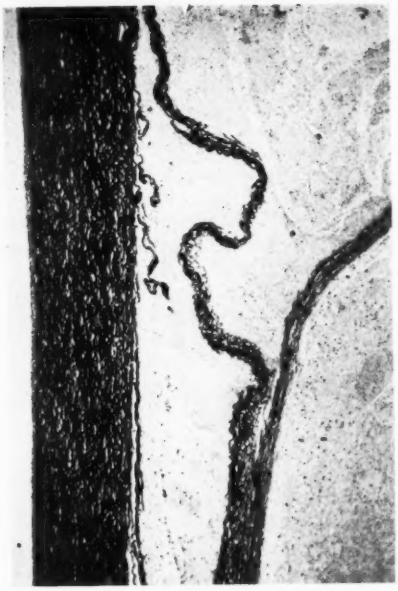

FIG. 2.—*Case* 2. From same section as Fig. 1, showing split in outer wall of aneurysm. The light grey granular appearance within and outside the aneurysm represents blood clot. (× 30.)

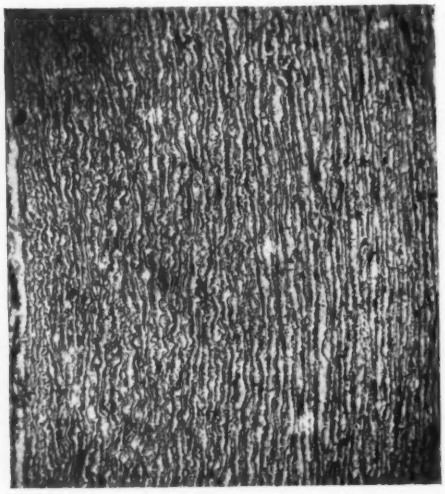

FIG. 3.—*Case* 2. Transverse section of unsplit part of aorta at level of aneurysm stained for reticulin by Gomori's method. Elastic tissue and mucoid material are unstained. (× 100.)

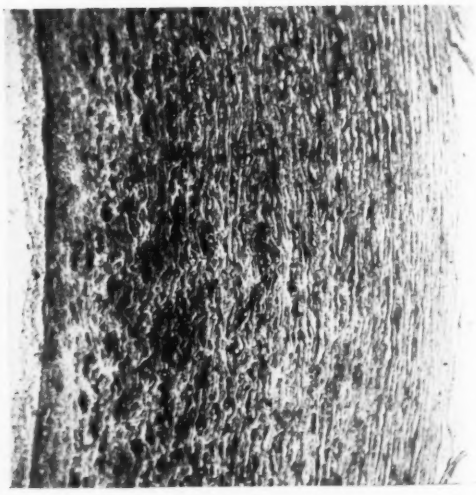

FIG. 4.—*Case* 2. Section near that shown in Fig. 3 showing dark mucoid material, most abundant in inner half of media (left half of figure). Hale's iron method. (× 100.)

The staining properties of the mucoid material are shown in the table. The green colour after Hale's method suggests the presence of acid mucopolysaccharides; the negative result after mucicarmine—a common finding—does not exclude the presence of substances of this type. The reddish-purple after toluidin blue suggests the presence of high molecular esters of polysulphuric acid, and the pink colour after the McManus technique (an application of the Schiff periodic acid reaction) can also be taken as evidence that mucopolysaccharides were present.

Discussion

Clinical diagnosis. The clinical diagnosis of dissecting aneurysm is beset with difficulties. The patient may not survive a dissection long enough for special investigation, or may be too ill to tolerate even a normal clinical examination. If a diagnosis is made, it is not unlikely to be coronary disease, and this may well be registered as the cause of death (Gardner *et al.*, 1939). Another probable diagnosis is that of an acute abdominal emergency, with laparotomy as a possible consequence.

Although the clinical picture of dissecting aneurysm is not constant, there is one characteristic symptom—namely a sudden attack of severe pain in the chest or abdomen (Holland and Bayley, 1940). No age is exempt; the youngest patient on record was 14 months old (Frei, quoted by Sailer, 1942), but medial lesions without dissection have been known to occur in a 12-day-old infant (Wolff, 1932); the oldest patient, noted by Shennan (1934), was nearly 100 years old.

Diagnosis at necropsy. If the patient comes to necropsy, the diagnosis is usually easy; in most cases there is a tear in the intima that should be obvious when the aorta is opened. In some cases, however, the intima is intact (Tyson, 1931; Mote and Carr, 1942) and the nature of the disease may then not be evident; hæmorrhage from a dissecting aneurysm that has ruptured through the adventitia may be attributed to some other source. It would therefore be a good practice to cut the aorta transversely after opening it longitudinally in all cases of sudden death without obvious cause, especially when there are signs of hæmorrhage in the thorax or abdomen.

Association with pregnancy. The association of dissecting aneurysm with pregnancy awaits explanation. Schnitker and Bayer (1944) found that of the 24 cases they considered, 6 occurred in the first six months, 14 in the last three months, 2 with labour pains, and 2 during the puerperium—one of them twelve days, the other three weeks post partum. Most of the cases thus occurred during the last three months of pregnancy and showed no special relation to labour. The dissection was therefore not attributable to the strain and blood-pressure changes associated with childbirth; a more likely factor was thought to be disturbed lipid metabolism, in particular the accumulation of cholesterol in the media. They recalled a similar association between dissecting aneurysm, post-operative hypothyroidism, and raised blood cholesterol. Another possible explanation is the softening of connective tissues that occurs in pregnancy, but whether the aorta is affected does not appear to be known.

Hereditary predisposition. The close relationship of our two patients suggests the possibility of a hereditary predisposition to dissecting aneurysm; both patients found physical exertion exhausting, which suggests that there may be a constitutional factor. The fact that the father and the four children of his first marriage are all healthy points to the second wife as the sole vector and it is regrettable that the cause of death of her premature child is not known. Our experience simply suggests that it would be worth while exploring the family history in cases of dissecting aneurysm.

Other possible ætiological factors. Physical exertion has long been considered as a possible factor in the production of dissecting aneurysm, especially in young patients (Wasastjerna, 1903). Exertion *per se*, however, is clearly an insufficient explanation, as otherwise dissecting aneurysms would be much commoner than they are. Reich (1944) notes that Willius and Cragg found hypertension in 80 per cent of cases of dissecting aneurysm, but adds that of 283 hypertensives studied by Thomas and Garber only 2 had dissecting aneurysms; from the hypertensive's point of view, dissecting aneurysm is therefore not a serious risk.

Ætiological significance of medial changes. The most important ætiological factor is now thought to be pathological changes in the aortic media. According to Sailer (1942), five main types of medial change may be associated with dissecting aneurysms: (1) fatty degeneration, fragmentation or necrosis of elastic tissue (sometimes with mucoid change), (2) hyaline degeneration of connective tissue, (3) fatty degeneration and atrophy of muscle, (4) necrosis of muscle (sometimes with mucoid change), and (5) primary mucoid infiltration with cyst formation (commonest in the ascending part of the aortic arch), which is illustrated by our Case 2.

This classification extends the work of Gsell (1928) and Erdheim (1929; 1930), who described the main

features of the medial change as patchy necrosis of muscle, mucoid degeneration with cyst formation, and repair of the media without signs of inflammation. Thus the pathological picture, which Erdheim (1930) finally designated *medionecrosis aortæ idiopathica cystica*, is not well defined, and the inter-relations and relative importance of the various changes are not clear. Amromin *et al.* (1948), however, regarded this varied morphology as the expression of a single morbid process—namely medial ischæmia. In support of their opinion they described narrowing of the vasa vasorum in 7 of 12 aortas with dissecting aneurysm, whereas in 20 control aortas only 2 showed narrowing of these vessels without medial and intimal changes in the aorta.

The interpretation of the significance of these medial changes is made more difficult by the fairly common finding of similar changes in the absence of dissecting aneurysms. Our own observations throw no light on the questions whether mucoid change may initiate a dissecting aneurysm or facilitate the course of the effused blood. The occurrence of mucoid change is not peculiar to the aorta; it may be found, for example, in the renal artery in some cases of hypertension, in arteries showing calcification of the media, and in the stroma of parotid tumours. It therefore seems possible that aortic mucoid may be merely a local manifestation of a more general change occurring in connective tissue. Since the mucoid material seen in our Case 2 did not resemble necrotic muscle or necrotic collagen, the possibility that mucoid change may be reversible is worthy of consideration.

To facilitate the study of medial changes and their possible relation to dissecting aneurysm, the changes seen in individual cases should be specified exactly; medionecrosis is a comprehensive term covering a variety of changes, and to apply it, for example, to the mucoid change seen in our Case 2 would be inappropriate and misleading.

Summary

Two cases of dissecting aneurysm of the aorta, one in a woman of 34, nine days after childbirth, the other in her 14-year-old son, are described. The relationship of the patients suggests the possibility of a hereditary predisposition to this disease.

The mother's aorta was not examined histologically and only part of the aneurysm from the boy was available for study. No lesion that might have initiated the dissection was found. Mucoid change was present in the inner media, but the dissection lay in the outer media.

The association between dissecting aneurysms and pregnancy may be due to the softening of connective tissues that occurs in pregnancy, and further work is needed to determine whether the aorta is among the organs affected. Mucoid change in the aorta may be simply one among many manifestations of a type of change occurring in intercellular tissues in general. The possibility that the change may be reversible is worthy of examination.

Clinically, dissecting aneurysm is likely to be mistaken for coronary disease or an acute abdominal emergency, its most characteristic feature being a sudden attack of severe pain in the chest or abdomen.

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References

Amromin, G. D., Schlichter, J. G., and Solway, A. J. L. (1948). *Arch. Path.*, **46**, 380.
Erdheim, J. (1929). *Arch. path. Anat.*, **273**, 454.
—— (1930). *Ibid.*, **276**, 187.
Gardner, E., Galbraith, A. J., and Hardwick, S. W. (1939). *Lancet*, **2**, 1019.
Gsell, O. (1928). *Arch. path. Anat.*, **270**, 1.
Hale, C. W. (1946). *Nature*, **157**, 802.
Holland, L. F., and Bayley, R. H. (1940). *Amer. Heart J.*, **20**, 223.
McManus, J. F. A. (1948). *Stain Technol.*, **23**, 99.
Mote, C. D., and Carr, J. L. (1942). *Amer. Heart J.*, **24**, 69.
Reich, N. E. (1944). *Clinics*, **3**, 346.
Sailer, S. (1942). *Arch. Path.*, **33**, 704.
Schnitker, M. A., and Bayer, C. A. (1944). *Ann. intern. Med.*, **20**, 486.
Shennan, T. (1934). *Med. Res. Counc. Spec. Rep. Ser.* No. 193.
Tyson, M. D. (1931). *Amer. J. Path.*, **7**, 581.
Wasastjerna, E. (1903). *Z. klin. med.*, **49**, 405.
Wolff, K. (1932). *Arch. path. Anat.*, **285**, 369.

THE VARIABILITY OF VENTRICULAR POTENTIALS AT THE DIAPHRAGMATIC LEVEL OF THE ŒSOPHAGUS

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The use of œsophageal electrocardiograms has been of value for semi-direct exploration of the electrical potentials derived from the posterior surface of the heart. Lieberson and Liberson (1934) reintroduced the method of œsophageal electrocardiography and described a qRs pattern that was considered a derivation from the posterior wall of the left ventricle. These observations were extended by Brown (1936) in an extensive study of the distribution of cardiac potentials in the œsophagus. In a review of the anatomy of the œsophagus, it was indicated that only a small segment of the lower part of the œsophagus at the level of the diaphragm was in relation to the " posterior basal surface of the left ventricle." Fluoroscopic control was considered to be essential in the positioning of the lowermost electrode at the ventricular level. Characteristically, the left ventricular surface pattern of a qRs was obtained at this level. The P wave was ill-defined and slurred and had lost the sharp intrinsic deflection that was characteristic of the P wave at the left atrial levels. Based on the premise that the posterior wall of the left ventricle could thus be explored, Hamilton and Nyboer (1938), and then Nyboer (1930, 1941, 1946) recommended the œsophageal lead for the diagnosis of posterior wall infarction. The " ventricular level " was judged by passing the œsophageal electrode a distance of 45 to 55 cm. from the nares or by the absence of the " auricular P wave " or by both these considerations. The presence of a deep Q and inverted T wave at the ventricular level was considered characteristic of posterior wall infarction. However, Helm *et al.* (1944) had difficulty in interpreting ventricular potentials at the lower end of the œsophagus, particularly with respect to the Q wave. They found that an endocardial potential like that normally recorded in the œsophagus at left atrial levels could extend to the ventricular level at the diaphragm. In this instance, the Q wave of endocardial origin would be a normal finding. Recently Burchell (1948) published data that also questioned the value of the œsophageal lead in the diagnosis of healed posterior wall infarction. Not only was it difficult to interpret the deep Q and inverted T waves at the level of the left ventricle, but a variety of electrocardiographic patterns were recorded at this level.

During an intensive study of intracardiac potentials in humans, conducted at the Mount Sinai Hospital for the past three years, a large number of patients with normal and abnormal electrocardiograms were studied. Œsophageal leads obtained in these patients revealed considerable variability of the ventricular complexes at the diaphragmatic level of the œsophagus—the so-called " ventricular level." From this large series of cases, several were selected because they illustrated the variability of the ventricular complex at the " ventricular level," and because they demonstrated the possibility of an erroneous interpretation of a deep Q wave. The findings in these selected cases were suitable to emphasize that the diaphragmatic segment of the œsophagus might often be in closer contact with the inferior vena cava, or the posterior caudad segment of the right atrium, than with the posterior basal wall of the left ventricle.

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METHOD

Serial œsophageal leads were obtained with a specially constructed œsophageal tube with 15 equidistant electrodes (1·75 cm. apart). The lowermost electrode was placed fluoroscopically at the diaphragmatic level (E1). A permanent record was obtained by means of a spot-film. Both intracardiac and præcordial reference leads were recorded simultaneously. The Sanborn tri-beam electrocardiograph was used in these studies.

RESULTS

Patients with Normal Hearts and Normal Electrocardiograms

Case 1. A man, 35 years of age, had a normal electrocardiogram, including extremity and chest leads. The ventricular complex at E1 (2·5 cm. below the level of the diaphragm) consisted of a rSR′ which was similar to the potential recorded in the right atrium in the region of the inferior vena cava. The P wave at E1 was ill-defined and lacked the intrinsic deflection, which was obtained at E4 over atrial levels (Fig. 1).

The positioning of E1 at the diaphragm and the absence of the intrinsic deflection in the P wave met the requirements of earlier workers for a true " ventricular level." Yet, at this " ventricular

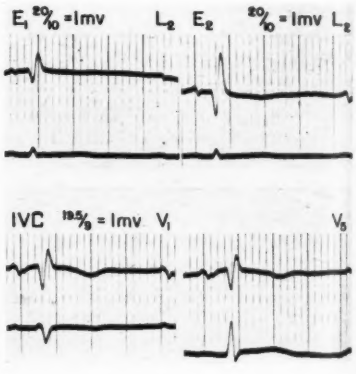
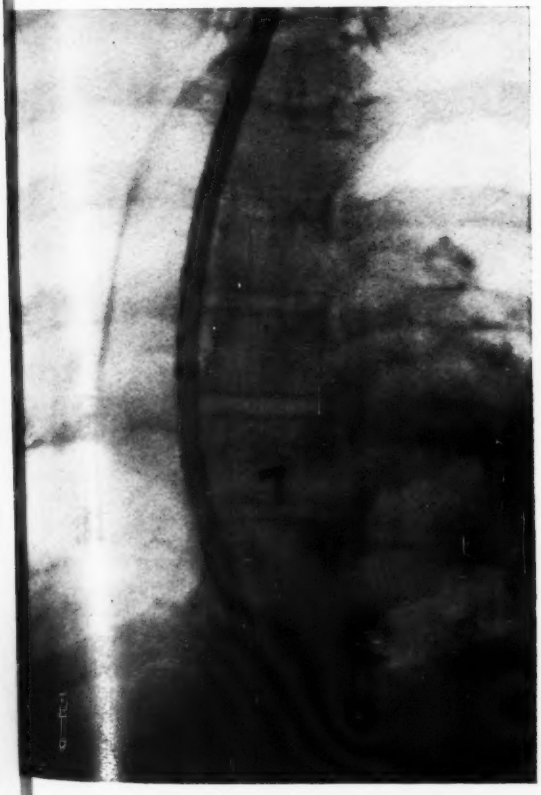


FIG. 1.—Case 1. Normal heart, and electrocardiogram. The exploring intracardiac electrode is in the region of the inferior vena cava. The ventricular complex at œsophageal leads E1 and E2 is similar to the complex recorded in the region of the inferior vena cava. With increased standardization an initial r is recorded; with normal standardization the rSR′ might have appeared to be a QR. The r is a reflection not of left ventricular surface but of right ventricular cavity or surface. The R′ is a reflection of late activation of the left ventricular surface.

level" and at the inferior vena cava an rSR′ was recorded which did not resemble the potentials usually derived from the free surface of the left ventricle (qRs). The rSR′ at the inferior vena cava and at E1 represented either right ventricular surface or cavity potential (rS) influenced in its terminal portion by left ventricular surface potential (R′). Furthermore, the r of the rSR′ pattern was visualized only because standardization was twice the normal (1 mv=20 mm.). With normal standardization (1 mv=10 mm.), the r would have been almost isoelectric and thus the rSR′ could have been mistaken for a QR.

Case 2. A woman, 19 years of age, had a normal electrocardiogram including extremity and chest leads. The ventricular complex at E1 (at the diaphragm) was essentially a W shaped complex preceded by an r. This basic rS pattern was similar to that recorded in the right atrium in the region of the inferior vena cava and represented either right ventricular surface or cavity potential. The interfering r′ which made the complex W shaped was derived from the left ventricular surface potential (r′ synchronous with R of V5). Again, the P wave at E1 was devoid of an intrinsic deflection which was present in the P wave at E3. The ventricular potential at this atrial level (E3) reflected left ventricular cavity potential (deep Q) (Fig. 2).



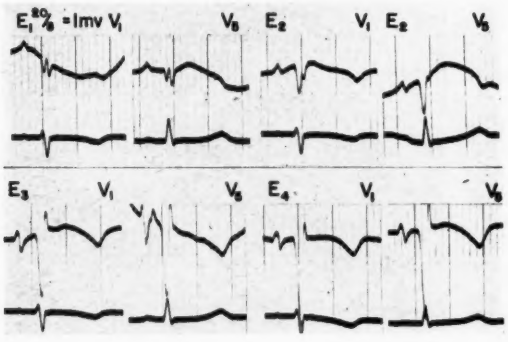


FIG. 2.—Case 2. Normal heart, and electrocardiogram. The exploring intracardiac electrode is in the region of the inferior vena cava. Œsophageal lead E1 is at the diaphragm. Basic rS pattern is recorded at œsophageal leads E1 and E2. r at E1 is almost synchronous with R at V5 and is derived from left ventricular surface potential. Without double standardization, the rSr′S′ would have appeared to be a QrS at E1 and a QS at E2.

In this normal patient, the ventricular potential at E1 again did not resemble a left ventricular surface potential. It was a mixed potential similar to the one recorded in the right atrium in the region of the inferior vena cava. Here again the r at E1 was recognized only because standardiza-

tion was doubled (1 mv=20 mm.) and simultaneous reference leads were taken. Without these, the rSr'S' at E1 might easily have been mistaken for a W shaped QS complex.

Case 3. A man, 47 years of age, had an electrocardiogram showing left axis deviation, S1, S2, and S3 being present. A broad R was recorded in aVR. At E1 (1·75 cm. below the diaphragm) an rS pattern was recorded. This pattern was also recorded at E2 and E3. The rS potential was similar to the potential recorded at the bottom of the right atrium. It represented right ventricular cavity or surface, and not left ventricular surface potential. The P wave at E1 still showed an intrinsic deflection (Fig. 3).

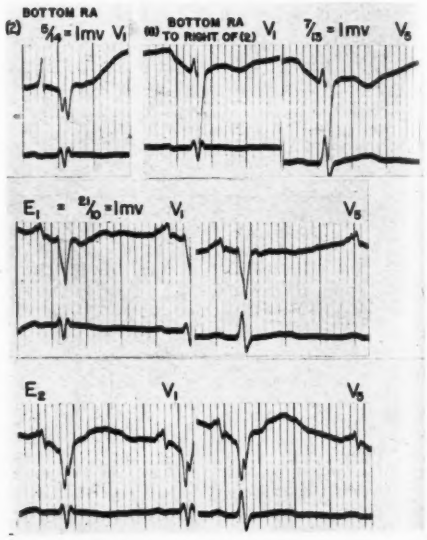


FIG. 3.—Case 3. Normal heart, and electrocardiogram. Note the position of the exploring intracardiac electrode to the left of the midline and its relation to the œsophagus. The rS pattern recorded at œsophageal lead E1 is similar to the potential in the right atrium at (2) and at (8). The initial r is seen at E1 because of double standardization.

In this normal patient, the exploring electrode in the right atrium extended past the mid-line. In the left oblique view the electrode was located posteriorly. The relationship of the exploring electrode in the right atrium to the œsophagus was clearly shown in the spot-film (Fig. 3). This close anatomical relationship of the right atrium to the œsophagus provided a basis for the similarity of potentials in the lower œsophagus and in the right atrium. It also accounted for the presence of an intrinsic deflection in the P wave at E1, which was below left atrial levels. Furthermore, the initial r of the ventricular complex at E1 was visualized only because standardization was doubled (1 mv=20 mm.). With normal standardization (1 mv=10 mm.), the r would have been almost isoelectric. The rS could have been mistaken for a QS.

Patient with Normal Heart and Partial Conduction Delay to the Right Ventricle

Case 4. A boy, 14 years of age. There was right axis deviation and the QRS measured 0·09 sec. The somewhat delayed R over the right side of the chest suggested a conduction delay to the right ventricle. At E1 (at the diaphragm) a QRS was recorded. The R at E1 was synchronous with the R at V5. The deep Q waves at E1, the bottom of the right atrium, and at V5 were synchronous.

FIG. 4.—Case 4. Normal heart. The exploring intracardiac electrode is at the bottom of the right atrium. Record 6 (Fig. 5) was taken at this point.

The ventricular potential at E1 (QRS) was similar to the potential recorded in the bottom of the right atrium (Fig. 4 and 5) and both reflected left ventricular cavity and surface potentials.

In this patient, without heart disease, but with a mild right ventricular conduction delay, a Q wave representing left ventricular cavity potential was recorded at the " ventricular level " (E1) and at the bottom of the right atrium. This Q wave at E1 most certainly was not a reflection of left ventricular cavity potential through a " window " of a posterior wall infarct. The R wave at E1, although recorded at the " ventricular level " represented only a remnant of the left ventricular surface potential.

Patients with Right Ventricular Hypertrophy

Case 5. A man, 59 years of age. There was right axis deviation. A broad delayed R′ was recorded in aVR and over the right side of the chest. The ventricular complex at E1 (1·75 cm. below the diaphragm) consisted of a QRs. The P wave at E1 was tall and showed an intrinsic deflection. The ventricular potential at E1 (QRs) was similar to the potential recorded at the bottom

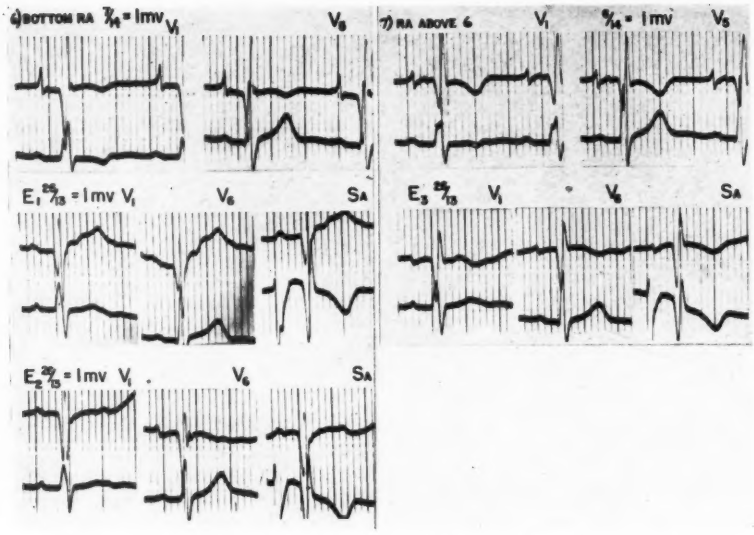


FIG. 5.—Case 4. Partial conduction delay in the right ventricle. The ventricular potentials at œsophageal leads E1 and E2 (QRS) are similar to those at the bottom of the right atrium (6). Œsophageal lead E3 is similar to the intracardiac potential recorded in the right atrium (7) just above (6). The conduction delay to the right ventricle (tall R–R′ at V1 in records 6 and 7) was accentuated during intracardiac catheterization. The Q wave at œsophageal lead E1 is unrelated to posterior wall infarction.

of the right atrium in the region of the inferior vena cava (Fig. 6). This pattern was also obtained at higher œsophageal levels (E2 to E6). The P wave at the " ventricular level " (E1), instead of being ill-defined, still showed an intrinsic deflection as it does over atrial levels. The Q wave recorded at E1, certainly was unrelated to a posterior wall infarct.

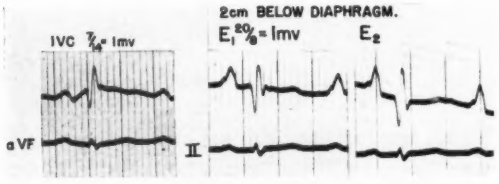


FIG. 6.—Case 5. Right ventricular hypertrophy. The QRs at œsophageal leads E1 and E2 are similar to the intracardiac potential recorded in the region of the inferior vena cava. The deep Q wave is unrelated to posterior wall infarction. The P wave at E1 still retains an intrinsic deflection.

In this patient, with pulmonary heart disease, spot-films clearly demonstrated that the catheter in the enlarged right atrium extended much to the left of the mid-line and overlapped the œsophagus. The posterior position of the catheter in the left oblique view corroborated the close relationship of the enlarged right atrium to the œsophagus. This finding provided an anatomical basis for the similarity of the cardiac potentials recorded in the lower end of the œsophagus and in the right atrium. The presence of an intrinsic deflection of the P wave at E1, presumably below left atrial levels, could also be explained by the close relationship of the right atrium to the œsophagus.

Case 6. A man, 58 years of age. There was right axis deviation. A broad delayed R′ was recorded in aVR. The delayed R′ over the right side of the chest was tall. The ventricular complex at E1 (at the diaphragm) consisted of a rSR′s′. This potential was similar to the potential recorded at the bottom of the right atrium (Fig. 7). Similar potentials were recorded in the œsophagus at higher levels (E2 to E8). The rSR′s′ in all probability reflected a mixture of right ventricular cavity

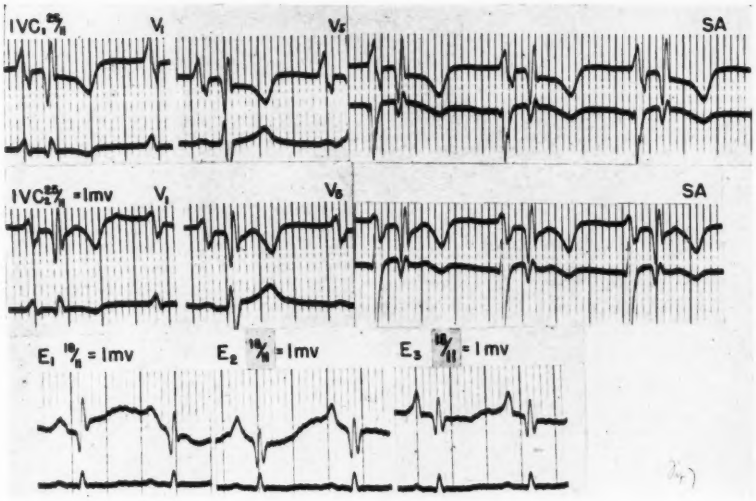


FIG. 7.—Case 6. Right ventricular hypertrophy. At œsophageal lead E1 an rSR's' is obtained which is similar to the intracardiac potential recorded at the bottom of the right atrium in the region of the inferior vena cava. This mixed potential reflects right ventricular cavity and surface potential. With normal standardization the initial r would have been isoelectric and would have been misinterpreted as a Q wave. The P wave at E1 still retains a sharp intrinsic deflection. IVC2 is at a slightly higher level than IVC1.

and surface potential. Without double standardization the initial r of this pattern would not have been recognized and the S wave would have been misinterpreted as a Q wave.

Case 7. A man, 46 years of age. Standard leads showed S1, S2 and S3. A broad delayed R' was recorded at aVR and over the right side of the chest. At E1 (at the diaphragm) there was an apparent QS pattern, the upstroke of which was interrupted by an R. This potential was similar to that recorded at the inferior vena cava where an rS pattern was recorded. The rS pattern was a reflection of right ventricular cavity. At E1, the P wave showed an intrinsic deflection (Fig. 8).

Once again in a patient with right ventricular hypertrophy, an apparent deep QS was recorded at E1. In reality this was an rS, but despite maximum amplification, the initial r was inconspicuous because of its very low voltage. Again, the type of P wave expected at higher atrial levels (with intrinsic deflection) was recorded at the " ventricular level."

Case 8. A man, 62 years of age. There was right axis deviation. The QRS complexes measured 0·09 sec.; TII and TIII were inverted. The extremity leads were not remarkable. A qRs pattern was recorded over the right chest. There was no Q wave over the left side of the præcordium. A QR pattern was recorded at E1 (at the diaphragm). This QR potential was similar to that recorded in the right atrium in the region of the inferior vena cava. At E3, the ventricular complex resembled that recorded in the right atrium at the tricuspid valve. Those QR potentials reflected a cavity Q and a surface R. It was difficult to decide whether the Q wave reflected right or left ventricular cavity, since no positive initial deflection was recorded in the right ventricular cavity. The absence of a Q wave over the left præcordium made it likely that the Q wave reflected right ventricular cavity (Fig. 9).

In this patient with right ventricular hypertrophy, a Q wave was recorded at E1 which was unrelated to posterior wall infarction. There was again evidence that the enlarged right atrium was in close relationship with the œsophagus and that similar potentials were recorded both in the right atrium and in the œsophagus.

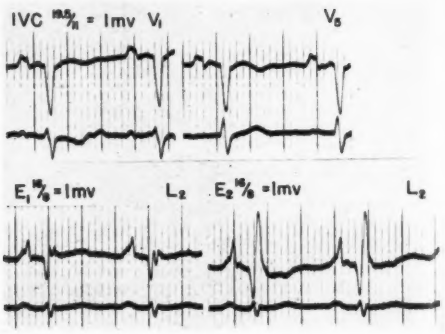


FIG. 8.—Case 7. Right ventricular hypertrophy. The exploring intracardiac electrode is in the region of the inferior vena cava. At œsophageal leads E1 and E2 there is a basic rS pattern. Even with maximum amplification, the r is tiny and S may be confused with a deep Q wave. The basic rS pattern is similar to the ventricular complex recorded in the region of the inferior vena cava. In this case, the rS represents right ventricular cavity potential. The P wave at E1 still shows a sharp intrinsic deflection.

Patient with Left Ventricular Hypertrophy

Case 9. A man, 52 years of age. There was left axis deviation. The electrocardiogram was typical of left ventricular hypertrophy. At E1 (at the diaphragm), an rS pattern was recorded (Fig. 10).

In this patient, the influence of left ventricular surface was to the left arm and left axilla. The left ventricular surface did not influence the potential in the lower part of the œsophagus. The rS at E1 reflected right ventricular cavity or surface potential.

DISCUSSION

The intimate anterior relationship of the œsophagus with the left atrium below the tracheal bifurcation is well known and has been described by Quain (1882), Piersol (1930), Gray (1942), and Cunningham (1943). The œsophagus actually leaves the spine at the fifth thoracic vertebra to lie close to the left atrium (Evans, 1936). Although veering slightly to the left at the level of the seventh thoracic vertebra, the œsophagus is still in close relationship anteriorly with the left atrium (Toldt, 1904; Eycleshymer and Schoemaker, 1911). From the eighth to the tenth thoracic vertebra, the œsophagus continues to the left and anteriorly to enter the abdomen through the diaphragm. This segment is actually the lower end of the œsophagus at the diaphragm, where the œsophageal lead (E1) is positioned in the cases of our study. The normal left ventricle is usually not listed as in anterior relation of the œsophagus in this region according to the authorities mentioned above and

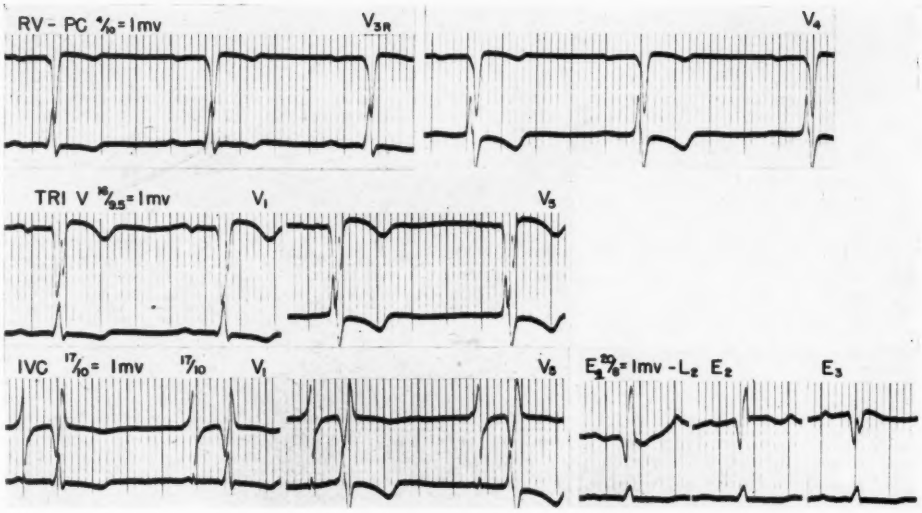


FIG. 9.—Case 8. Right ventricular hypertrophy. A QR pattern is obtained at œsophageal lead E1 which is similar to the intracardiac potential recorded in the region of the inferior vena cava. At the tricuspid valve region, there is a QS pattern similar to the pattern at E3, where the upstroke is interrupted by an R wave. A QS is recorded in the cavity of the right ventricle. The Q wave in œsophageal leads is unrelated to posterior wall infarction.

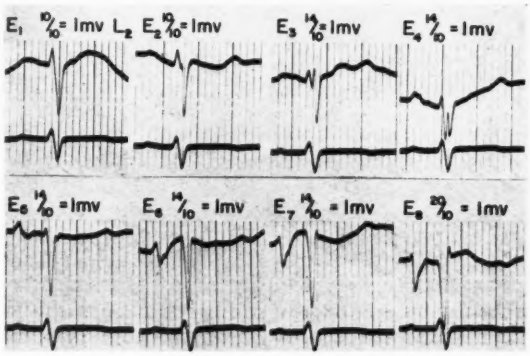


FIG. 10.—Case 9. Left ventricular hypertrophy. An rS pattern is recorded at œsophageal lead E1. The rS reflects right ventricular cavity or surface potential. Q waves are recorded in the œsophageal leads with the appearance of an intrinsic deflection in the atrial complexes.

to Evans (1936). However, Rigler (1929) maintains that the œsophagus is in contact with " a small portion of the left ventricle " for 2 to 3 cm. above the diaphragm. Brown (1936) refers to the serial cross-sections of Eycleshymer and Schoemaker (1911) as anatomical proof that an electrode in the œsophagus at the diaphragm is " closer to the base of the left ventricle than is a præcordial lead to the surface of the right ventricle." Brown stresses this left-anterior relationship to the left ventricle, but only mentions the possibility of a right-anterior relationship of the œsophagus to the right atrium at the inferior vena cava.

Our findings seem to indicate that the relationship of the œsophagus to the right and anteriorly

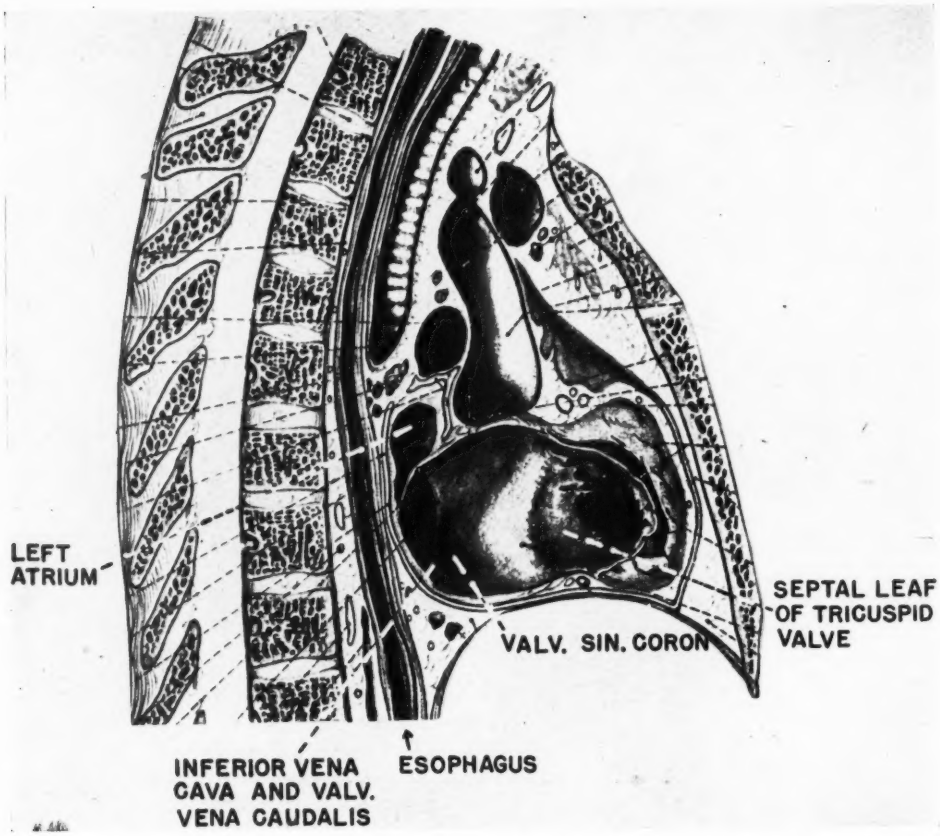


FIG. 11.—Median sagittal section of thorax (from Pernkopf).

with the inferior vena cava and at times with the right atrium is often important for the understanding of potentials obtained at the diaphragm. Both Eycleshymer and Schoemaker (1911), and Pernkopf (1937) clearly demonstrate in their cross-sections that, at the diaphragm, the close cardiac relationships of the œsophagus to the right and anteriorly are (1) the atrio-ventricular groove and (2) the bottom of the right atrium in the region of the inferior vena cava (Fig. 11 and 12). The spot-films of Case 3 (Fig. 3) illustrate this point. These right anterior relationships seem to be predominant in our normal patients, who show similar potentials in the œsophagus at E1, and in the right atrium in the region of the inferior vena cava. In these selected normal patients, the influence of the free left ventricular surface on the ventricular complex is minimal. The factor of anatomical relationship to the right atrium is even more evident in the cases of pulmonary heart disease with right atrial enlargement. In Case 5, the spot-films of the position of the catheter indicate the extension of the enlarged right atrium posteriorly and to the left beyond the mid-line. The relationship of this left-posterior extension of right atrium to the lower end of the œsophagus explains the similarity of ventricular potentials obtained at E1 and at the bottom of the right atrium in the region of the inferior vena cava. The presence of an intrinsic deflection in the P wave at E1 may also be attributed to this close anatomical relationship.

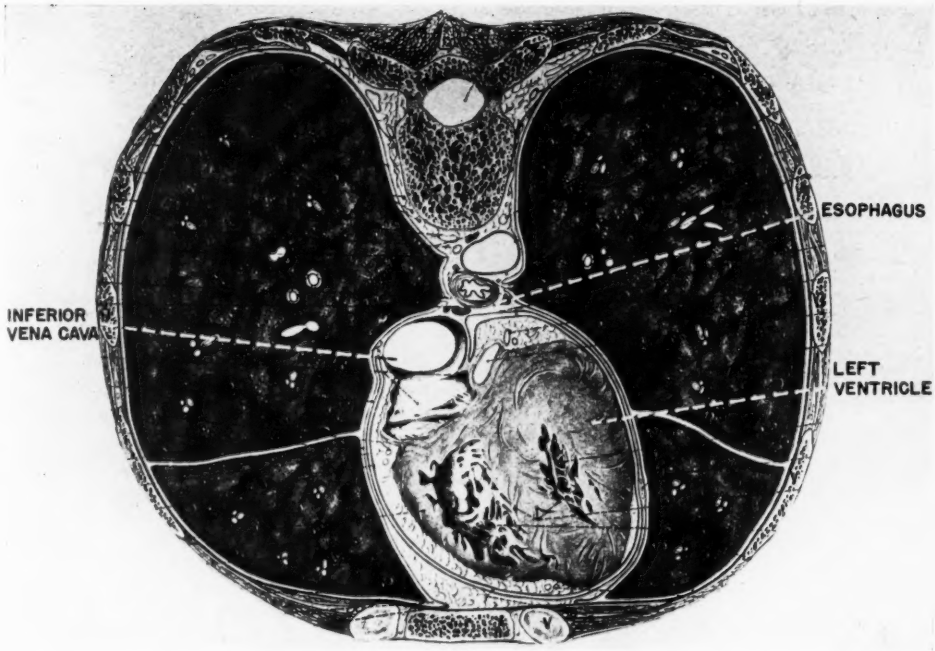


FIG. 12.—Cross-section of thorax at level of 9th thoracic vertebra (from Pernkopf).

The variability of the ventricular potential in the œsophagus at the diaphragm is common. When the ventricular potential does not reflect the free left ventricular surface (qRs), it may reflect either right ventricular surface or cavity (rS), and at times left ventricular cavity (QS) without the " window " effect of an infarct. In order to detect an initial r wave and to avoid confusion with a Q wave, adequate amplification of the œsophageal potential is necessary. As a further precaution, præcordial reference leads (V1 and V5) should be recorded simultaneously with œsophageal leads.

SUMMARY AND CONCLUSIONS

The ventricular potential at the diaphragmatic level of the œsophagus, the so-called " ventricular level " may not reflect free left ventricular surface (qRs), as has been assumed in the past.

The variability of ventricular potentials at the diaphragmatic level of the œsophagus (E1) has been illustrated in a selected series of patients with (1) normal electrocardiograms, (2) normal heart with partial conduction delay to the right ventricle, (3) right ventricular hypertrophy, and (4) left ventricular hypertrophy. These potentials were either rS or QS in type and were similar to the potentials recorded in the right atrium at the inferior vena cava.

There is a close anatomical relationship of the diaphragmatic segment of the œsophagus, anteriorly and to the right, with the right atrium in the region of the inferior vena cava. This relationship is even more accentuated in the presence of right atrial enlargement, as in pulmonary heart disease or congestive failure. This anatomical relationship is the ætiological factor underlying the similarity of potentials recorded at E1 and in the right atrium at the inferior vena cava.

These potentials may reflect surface or cavity of the right ventricle (rS). At times, left ventricular cavity (QS) is tapped without the presence of posterior wall infarction.

Simultaneous præcordial reference leads and adequate amplification are necessary in order to determine the presence of an initial r wave at E1 and so to avoid the misinterpretation of a Q wave.

References

Brown, W. H. (1936). *Amer. Heart J.*, **12**, 1.
Burchell, H. B. (1948). *Amer. J. med. Sci.*, **216**, 492.
Cunningham, D. J. (1943). *Textbook of Anatomy*, 8th ed. Oxford University Press, London.
Evans, W. (1936). *The Course of the Œsophagus in Health, and in Disease of the Heart and Great Vessels.* Great Britain Privy Council, Med. Res. Council, Spec. Rep. Series No. 208.
Eycleshymer, A. C., and Schoemaker, D. M. (1911). *A Cross-Section Anatomy*, Sec. 25–27, D. Appleton and Co., New York.
Gray, H. (1942). *Anatomy of the Human Body*, 24th ed. Lea and Febiger, Philadelphia.
Hamilton, J. G. M., and Nyboer, J. (1938). *Amer. Heart J.*, **15**, 414.
Helm, J. D. Jr., Helm, G. H., and Wolferth, C. C. (1944). *Ibid.*, **27**, 755.
Lieberson, A., and Liberson, F. (1934). *Proc. Soc. exp. Biol.*, N.Y., **31**, 441.
Nyboer, J. (1939). *J. Clin. Invest.*, **18**, 495.
—— (1941). *Amer. Heart J.*, **22**, 469.
—— (1946). *Tr. A. Life Insur. M.Dir. America*, **30**, 31.
Pernkopf, E. (1937). *Topographische Anatomie des Menschen, Urban and Schwarzenberg*, Vol. 1, Berlin and Vienna.
Piersol, J. A. (1930). *Human Anatomy*, J. B. Lippincott and Co., Philadelphia and London.
Quain, R. (1882). *Elements of Anatomy*, 9th ed. William Wood and Co., New York.
Rigler, L. G. (1929). *Amer. J. Roentgen.*, **21**, 563.
Toldt, C. (1904). *An Atlas of Human Anatomy for Students and Physicians*, Rebman, Ltd.

THE LUNG VOLUME IN LOW OUTPUT CARDIAC SYNDROMES

BY

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During the past four years lung volume studies have been carried out in this department on a large series of normal subjects and on many victims of cardiac and respiratory disease. Some findings have been published elsewhere (Whitfield, Waterhouse, and Arnott, 1950*a*, *b*, and *c*) and this paper concerns the results obtained in patients with low output cardiac syndromes.

The lung volume in heart disease has been studied by several workers but their results have been to some extent at variance and were obtained before simple methods of measuring cardiac output were available. Over 30 years ago Peabody and Wentworth (1917) found the vital capacity to be decreased below 90 per cent of normal (predicted from the surface area) in 131 of their 156 unspecified cardiacs. The shrinkage in vital capacity was greatest in the decompensated patients and their working capacity and expectation of life decreased in proportion to the fall in their vital capacity. McClure and Peabody (1917) in a study of 24 patients with "heart disease" confirmed that the vital capacity decreased with the degree of congestive failure and increased again as the patients came out of failure, returning to normal only if full compensation was restored. Brittingham and White (1922) reached exactly similar conclusions from a study of 48 patients with "heart disease." Pearce (1917) reported one case of decompensated heart disease in which the vital capacity diminished as the cardiac output fell. Peters and Barr (1921) determined all the divisions of lung volume in six patients with "heart disease" and compared the results obtained with the predicted volumes, using Lundsgaard's three-dimensional chest measurements for the purpose of prediction. Of the 6 patients, 5 who were decompensated showed diminished total lung volumes and vital capacities; in 3 of the 5 the residual air was reduced and in the other 2 it was normal. The one compensated case showed a slightly reduced total lung volume and vital capacity and a normal residual air. Lundsgaard (1923) in a study of 11 cases of "heart disease" (3 decompensated and 8 compensated) found the vital capacity decreased in all, especially those in failure; the total lung volume and residual air were also decreased in the decompensated cases but the residual air was substantially increased in those not in failure. Binger (1923) used West's surface-area formula for the vital capacity and from it predicted the other lung volume divisions. In 11 cases of rheumatic heart disease, dyspnœic on the slightest exertion but not in actual failure, he found the vital capacity diminished and the residual air increased, but when decompensation supervened the vital capacity further diminished but the residual air sometimes became greater and sometimes less. Meakins and Christie (1929) confirmed the correlation between the reduction in vital capacity and the degree of dyspnœa and also found a virtual disappearance of the reserve air and an increase in the residual air/total lung volume ratio in heart failure, the latter increasing and decreasing pari passu with the degree of decompensation. Altschule *et al.* (1943) studied the postural changes in lung volume in low output cardiacs and found them similar to those occurring in normal subjects.

Methods

Studies were made of 26 patients suffering from rheumatic heart disease, hypertension, or coronary artery disease. They were first assessed clinically and radiologically, and then grouped for statistical purposes according to their state of compensation. The first group comprised 8 cases all well compensated and with a normal or moderately reduced exercise tolerance (i.e. Grade I and II). In the second group were 3 patients who were dyspnœic on the slightest exertion but showed no other objective evidence of congestive cardiac failure (grade III). The third group of the remaining ten cases were in congestive failure (grade IV). Fuller details of each group are given in Table I. With patients in the sitting position the vital

capacity, complemental air, and reserve air were measured on a Benedict-Knipping spirometer in the usual way and the functional residual air was determined by the closed circuit constant volume hydrogen (or helium) dilution method described by McMichael (1939). The residual air was obtained by subtracting the reserve air from the functional residual air.

TABLE I

SEX, AGE, AND AETIOLOGICAL DISTRIBUTION

State of Compensation	No.	Age (years)		Sex	Rheumatic Disease	Hyper-tension	Coronary Disease
		Mean	Range				
Grade I or II	8	27·3	15–46	3M, 5F	7	1	—
Grade III	8	39·3	19–55	3M, 5F	4	2	2
Grade IV	10	41·7	13–66	5M, 5F	5	2	3

RESULTS

In a previous communication (Whitfield *et al.*, 1950*c*) the correlation in normal subjects between the lung volume and age, height, weight, chest expansion and radiological chest volume was reported and multiple regression equations by which the total lung volume and its subdivisions could be predicted from these five variables were given. In congestive cardiac failure the radiological chest volume is likely to be reduced by ascitic fluid and hepatic engorgement producing upward displacement of the diaphragm, and dyspnœa will often prevent full chest expansion. In this series of cases we have therefore only considered age, height and weight and from these have predicted what the lung volume would have been had they been normal subjects. The predicted absolute values thus obtained and the actual results of spirometry are shown for each of the three groups in Table II.

TABLE II

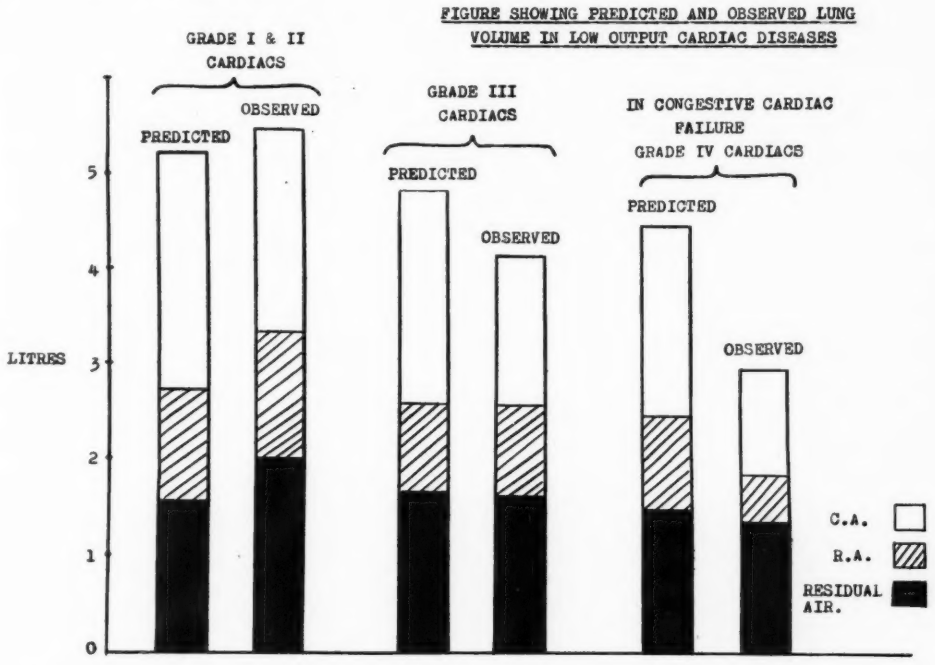
PREDICTED AND OBSERVED ABSOLUTE LUNG VOLUMES

Group	Division of Lung Volume	Males			Females			Males and Females				
		Observed	Predicted	Difference	Observed	Predicted	Difference	Observed	Predicted	Difference	S.E. of Mean	p
Grade I and II cardiacs 3M, 5F	T.L.V. ..	6·38	6·09	+0·29	4·95	4·69	+0·26	5·48	5·21	+0·27	0·23	0·25
	V.C. ..	4·12	4·37	−0·25	3·10	3·22	−0·12	3·49	3·65	−0·16	0·18	0·37
	C.A. ..	2·42	3·01	−0·59	1·99	2·19	−0·20	2·15	2·50	−0·35	0·13	0·005
	R.A. ..	1·71	1·36	+0·35	1·11	1·02	+0·09	1·34	1·15	+0·19	0·13	0·13
	F.R.A. ..	3·96	3·08	+0·88	2·96	2·49	+0·47	3·33	2·71	+0·62	0·19	0·001
	Resid. Air	2·26	1·72	+0·54	1·84	1·47	+0·37	2·00	1·56	+0·44	0·16	0·001
Grade III cardiacs 3M, 5F	T.L.V. ..	4·71	5·68	−0·97	3·78	4·30	−0·52	4·13	4·82	−0·69	0·23	0·003
	V.C. ..	2·78	3·53	−0·75	2·37	2·97	−0·60	2·53	3·18	−0·65	0·18	0·0003
	C.A. ..	1·71	2·58	−0·87	1·48	2·03	−0·55	1·57	2·24	−0·67	0·13	<0·0001
	R.A. ..	1·07	0·96	+0·11	0·89	0·93	−0·04	0·96	0·94	+0·02	0·13	0·13
	F.R.A. ..	3·00	3·10	−0·10	2·29	2·26	+0·03	2·56	2·58	−0·02	0·19	0·29
	Resid. Air	1·93	2·15	−0·22	1·40	1·33	+0·07	1·60	1·64	−0·04	0·16	0·13
In Congestive failure Grade IV cardiacs 5M, 5F	T.L.V. ..	3·14	4·76	−1·62	2·73	4·16	−1·43	2·94	4·46	−1·52	0·22	<0·0001
	V.C. ..	1·58	3·04	−1·46	1·58	2·93	−1·35	1·58	2·98	−1·40	0·16	<0·0001
	C.A. ..	1·07	2·06	−0·99	1·16	2·00	−0·84	1·12	2·03	−0·91	0·12	<0·0001
	R.A. ..	0·51	0·98	−0·47	0·42	0·93	−0·51	0·46	0·95	−0·49	0·12	<0·0001
	F.R.A. ..	2·07	2·70	−0·63	1·57	2·16	−0·59	1·82	2·43	−0·61	0·18	0·0007
	Resid. Air.	1·56	1·72	−0·16	1·15	1·23	−0·08	1·36	1·48	−0·12	0·15	0·42

In Grades I and II it will be seen that the most striking changes are an increase in the functional residual air and residual air and a decrease in the complemental air with a consequent elevation of the resting respiratory level. The total lung volume, vital capacity, and reserve air are not materially altered. In Grade III the functional residual air and residual air return to normal and the reserve air is again unchanged, but there is an even greater reduction in complemental air which is reflected in a highly significant reduction in the vital capacity and total lung volume.

In congestive cardiac failure there is a highly significant reduction in all divisions of lung volume except the residual air which remains the same as the predicted value. These changes are shown diagrammatically in the figure.

FIGURE SHOWING PREDICTED AND OBSERVED LUNG VOLUME IN LOW OUTPUT CARDIAC DISEASES



In order to amplify these findings the lung volume determination of seven patients of the third group was repeated when their degree of failure was appreciably greater or less than it had been at the time of the first measurement. The results are shown in Table III, which shows that there is a shrinkage in all divisions of lung volume (including the residual air) as the degree of cardiac failure increases. While this is in accord with the conclusions reached from study of the predicted and observed lung volumes the reduction only attains statistical significance in the case of the vital capacity, reserve air and functional residual air, owing to the small number of patients and the fact that the change in clinical state was sometimes not great.

In 4 of the 7 patients more than two lung volume determinations were made and an example is shown in Table IV which gives details in the case of a man of 66 with aortic stenosis and incompetence who was first admitted in congestive failure in February, 1950, and became fully compensated again with rest and digitalis only to be readmitted in gross failure in August, 1950, and to die a few days later. The progressive increase in all lung volume divisions as the degree of cardiac failure diminished and their gross reduction in extreme failure is very striking. The changes in the residual air volume are particularly well shown. The predicted residual air for this subject was

TABLE III

MEAN DIFFERENCES IN PAIRED OBSERVATIONS OF ABSOLUTE LUNG VOLUME OF SEVEN "LOW-OUTPUT" CARDIACS RE-EXAMINED WHEN DEGREE OF FAILURE HAD CHANGED

Division of Lung Volume	Difference between Lesser and Greater Decompensation Values (litres)	Standard Error of Mean	p
Total Lung Volume ..	0·70	0·30	0·06
Vital Capacity	0·38	0·15	0·05
Complemental Air ..	0·18	0·13	0·21
Reserve Air	0·20	0·06	0·01
Functional Residual Air	0·52	0·18	0·03
Residual Air	0·32	0·16	0·09

TABLE IV

LUNG VOLUME DETERMINATIONS OF ONE "LOW-OUTPUT" CARDIAC IN VARYING DEGREES OF DECOMPENSATION

Date	Clinical State	Absolute Values (litres)						Percentage of T.L.V. Values				
		T.L.V.	V.C.	C.A.	R.A.	F.R.A.	Residual Air	V.C.	C.A.	R.A.	F.R.A.	Residual Air
22/2/50	Gross œdema	3·29	1·54	1·16	0·38	2·13	1·75	47	35	12	65	53
6/3/50	Slight œdema	3·72	1·80	1·34	0·46	2·38	1·92	48	36	12	64	52
8/3/50	No œdema	4·21	2·08	1·43	0·65	2·78	2·13	49	34	15	66	51
3/8/50	Gross œdema: right pleural effusion	1·91	0·97	0·64	0·33	1·27	0·94	51	33	18	67	49

1·93 litres and the observed values show an increase of 200 ml. when not in failure, a normal value in moderate failure and a reduction of one litre when failure was gross. Admittedly the right pleural effusion is an obvious factor contributing to this reduction.

It seems clear, therefore, that in compensated low output cardiac syndromes there is an elevation in the resting respiratory level, a diminution in complemental air, and an increase in functional residual air, and residual air, the remaining divisions of lung volume being unaltered. As decompensation supervenes the residual air volume returns to normal, the complemental air becomes progressively smaller and in actual failure the reserve air is also diminished. The diminution in complemental air accounts for the reduction in vital capacity and total lung volume and in failure this reduction is accentuated by the fall in reserve air which also produces diminution in the functional residual air. In failure the reduction in the various lung volume divisions becomes greater as the degree of cardiac failure increases and in severe failure the residual air is reduced to subnormal levels.

The problem is how these changes are mediated. Lundsgaard (1923) and Binger (1923) considered that the increased residual air (and the diminished vital capacity) in fully compensated heart disease is due to the increased volume of blood in the pulmonary circulation producing a "stiff lung" (Lungenstarre) with consequent inability to empty the lungs in a normal manner. That an increase in the volume of blood in the lungs would have such an effect has been demonstrated experimentally in cats by Drinker *et al.* (1922) and in dogs by Mack *et al.* (1947). However, Borden *et al.* (1949) have shown that in compensated mitral stenosis the volume of blood in the pulmonary vascular bed is normal, and during cardiac catheterizations we ourselves have observed a normal pressure in the smaller pulmonary arteries in cases of mitral stenosis where the right ventricular pressure has been high. The explanation of the lung volume changes in compensated

low output cardiac syndromes therefore remains enigmatic and will probably continue so until the mechanism of the lesser circulation is better understood.

The explanation of the lung volume changes that are found in low output cardiac failure are less open to dispute. Binger (1923) considered them to arise partly from distended lung capillaries and œdema encroaching on alveolar spaces (Lungenschwellung) and partly from the increased heart size and the upward displacement of the diaphragm by ascites and hepatic enlargement reducing the thoracic space available to the lungs. There seems little doubt that these are major factors and in addition the increased total blood volume in cardiac failure (Meneely and Kaltreider, 1943) and the transudation of fluid into some alveolar spaces must play a significant part. Furthermore, hydrothorax when present, will also reduce the thoracic space available for the lungs.

To ascertain the part played by heart size in the production of the lung volume changes in low output cardiac disease we have measured the cardio-thoracic ratio and also the ratio between the radiological cardiac area and the radiological chest area on the postero-anterior radiographs of 22 of our cases and have calculated their correlation with the differences between predicted and observed lung volume found in each case. The results obtained are shown in Table V. The radiological cardiac area and radiological chest area were measured with a planimeter and at least two measurements were made in each case.

TABLE V

CORRELATION COEFFICIENTS OF DIFFERENCES BETWEEN OBSERVED AND PREDICTED VALUES OF LUNG VOLUME AND HEART SIZE IN 22 LOW OUTPUT CARDIACS

Division of Lung Volume	Cardio-Thoracic Ratio	Radiological Cardiac Area–Radiological Chest Area Ratio
Total Lung Volume	−0·694	−0·794
Vital Capacity	−0·647	−0·676
Complemental Air	−0·515	−0·462
Reserve Air	−0·571	−0·666
Functional Residual Air	−0·606	−0·752
Residual Air	−0·453	−0·593

Significance levels (n=32: 0·4237=5%; 0·492=2%; and 0·537=1%

It will be seen that the differences between the observed and predicted values of all the divisions of lung volume show a significant negative correlation with both the cardio-thoracic ratio and the radiological cardiac area/radiological chest area ratio. In all but three instances the degree of correlation is high ($p=<0{\cdot}01$). This means that as the maximum transverse diameter of the heart increases relative to the maximum transverse diameter of the thorax and as the proportion of the radiological chest area occupied by the heart increases so the various divisions of lung volume become increasingly lower than their predicted values. In other words the size of the heart is significantly correlated with, and probably an important factor in the production of the lung volume changes found in low output cardiac disease. The correlation coefficients, however, do not suggest that the burden of increased heart size is borne by any particular fraction of lung volume but rather that it operates, as would be anticipated, by reducing the thoracic space available to the lungs.

SUMMARY

The total lung volume and all its subdivisions have been determined in 26 "low output" cardiac patients in varying degrees of compensation. Predicted values have also been calculated from age, height, and weight.

Fully compensated cases show an increase in functional residual air and residual air, a decrease

in complemental air, and an elevation of the resting respiratory level. The cause of these changes is uncertain and the hypothesis of " Lungenstarre " involves dubious assumptions and is open to question.

As failure supervenes the complemental air further diminishes and the reserve air becomes less than normal; the functional residual air shrinks to subnormal levels and in extreme failure the volume of residual air is reduced. These changes result in marked diminution of the vital capacity and total lung volume.

Increased heart size is an important factor in the production of these changes and operates by reducing the thoracic space available for the lungs.

In low output cardiac failure the diminution in the various divisions of lung volume is in direct relation to the degree of failure.

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REFERENCES

Altschule, M. D., Zamcheck, N., and Iglauer, A. (1943). *J. clin. Invest.*, **22**, 805.
Binger, C. A. L. (1923). *J. exp. Med.*, **38**, 445.
Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S. (1949). *J. clin. Invest.*, **28**, 1138.
Brittingham, H. H., and White, P. D. (1922). *J. Amer. med. Ass.*, **79**, 1901.
Drinker, C. K., Peabody, F. W., and Blumgart, H. L. (1922). *J. exp. Med.*, **35**, 77.
Ebert, R. V., Borden, C. W., Wells, H. S., and Wilson, R. H. (1949). *J. clin. Invest.*, **28**, 1134.
Lundsgaard, C. (1923). *J. Amer. med. Ass.*, **80**, 163.
Mack, I., Grossman, M., and Katz, L. N. (1947). *Federation. Proc.*, **6**, 161.
McClure, C. W., and Peabody, F. W. (1917). *J. Amer. med. Ass.*, **69**, 1954.
McMichael, J. (1939). *Clin. Sci.*, **4**, 167.
Meakins, J. C., and Christie, R. V. (1929). *Ann. intern. Med.*, **3**, 423.
Meneely, G. R., and Kaltreider, N. L. (1943). *J. clin. Invest.*, **22**, 521.
Peabody, F. W., and Wentworth, J. A. (1917). *Arch. intern. Med.*, **20**, 443.
Pearce, R. G. (1917). *J. Amer. med. Ass.*, **69**, 1954.
Peters, J. B., and Barr, D. P. (1921). *Amer. J. Physiol.*, **54**, 335.
Whitfield, A. G. W., Waterhouse, J. A. H., and Arnott, W. M., (1950*a*). *Brit. J. Soc. Med.*, **4**, 1.
——, ——, —— (1950*b*). *Ibid.*, **4**, 86.
——, ——, —— (1950*c*). *Ibid.*, **4**, 113.

ENDOCARDIAL FIBROSIS

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Fibrosis of the myocardium and endocardium causing chronic cardiac failure is most frequently seen with disease of the coronary arteries. Occasional cases occur, however, where the blood vessels are normal and among these a group may be recognized in which fibrosis is confined to the endocardium and to the myocardium immediately underlying it. The pathological and clinical features of this condition are to be described and two further cases reported.

The endocardium is thickened and opaque and there is often mural thrombosis. Fibrous tissue extends into the myocardium along the thebesian veins, and there is necrosis and replacement fibrosis confined to the adjacent muscle. Inflammatory changes are not found and endocardial fibrosis seems a suitable descriptive term.

Most cases occur in young adults but it has been described in children, and some cases are recorded as idiopathic hypertrophy of the heart (Kugel and Stoloff, 1933; Mahon, 1936). The onset is insidious with congestive cardiac failure. There is often a slight fever. The heart is enlarged, but the cardiac impulse is weak and the blood pressure low. Systolic murmurs and occasionally thrills have been described. Sooner or later gallop rhythm appears and frequently alternation of the pulse. Emboli from mural thrombus may obstruct small or large arteries. The electrocardiogram is abnormal, usually showing low voltage curves, and flat or inverted T waves in one or more leads. The rhythm is usually regular but disorders of rhythm and conduction occasionally occur. If mural thrombosis does not occur the disease may last for several years. Improvement often occurs with rest and treatment but a fatal outcome is inevitable. If massive intra-cardiac thrombosis takes place, the effective ventricular cavity becomes greatly decreased and death occurs from rapidly developing cardiac failure or multiple emboli.

The earliest account of the condition is that of Josserand and Gallavardin in 1901 who described it as primary subacute myocarditis and recorded three cases. In 1914 a further case in which progressive cardiac failure was accompanied by multiple embolic accidents was reported by Roque and Levy and yet another by Gallavardin and Gravier in 1929. A single case was fully described from the pathological standpoint by Boikan (1931) as myocarditis perniciosa and he contrasted the findings with those in the recognized forms of myocarditis. In 1936 Loeffler described a syndrome of endocarditis parietalis fibroplastica with eosinophilia and reported two cases which conform closely with the condition under discussion, and further examples of this were recorded by Mumme (1940) and Egger (1944). The earliest cases in America were reported by Levy and Rouselot (1933) as cardiac hypertrophy of unknown aetiology in young adults. Three cases with great cardiac enlargement, endocardial fibrosis and multiple emboli from mural thrombosis were described. Three out of five cases of cardiac failure of unknown cause recorded by Reisinger and Blumenthal (1941) appear to be examples of endocardial fibrosis, and three cases were described in detail by Smith and Furth (1943) as fibrosis of endocardium and myocardium with mural thrombosis. Further reports appeared under the titles of diffuse isolated myocarditis (Toreson,

1944) and chronic fibroplastic myocarditis (Ware and Chapman, 1947) and a pathological study of two cases of Flynn and Mann (1946) drew attention to the effects of endocardial fibrosis on the blood supply of the adjacent myocardium.

The condition was always considered uncommon until 1946 when Bedford and Konstam briefly described forty cases encountered in the Middle East in West African soldiers. Necropsy confirmed the diagnosis of endocardial fibrosis in seventeen of them. In 1948 Davies described the pathological findings in fifty-two cases in East Africa where it is the cause of 10 per cent of all cases of cardiac failure, and Edge (1946) described a case in a European soldier who fell ill while stationed in West Africa.

The prevalence of this disease in Africa may shed light on its cause, and its recognition in Europeans spending a relatively short period there may also be significant. Two further cases of endocardial fibrosis in Europeans living in West Africa are to be described.

Case 1. A 40-year-old doctor who had served in Nigeria in the Colonial Medical Service for 9 years. He had jaundice in 1936 following yellow-fever immunization, and one attack of malignant tertian malaria, and early in 1944 had swellings of the arms attributed to loa-loa. He began to feel unwell in August, 1944, and was found to have an eosinophilia of 35 per cent. In January, 1945, he first had attacks of dyspnœa and cough relieved by injections of neoarsphenamine. An enlarged axillary gland was removed which showed lymphoid hyperplasia with eosinophylic infiltration. In April, 1945, he noticed low fever, aching in the limbs and chest, and increasing dyspnœa on effort. He returned to England in June and on July 3, 1945, was admitted to St. Thomas' Hospital.

On admission: T. 99·0; P. 100 (regular); R. 25; B.P. 115/95. Examination showed a well-nourished man who was dyspnœic and had signs of congestive cardiac failure. The heart was enlarged five inches to the left and a soft systolic murmur and a protodiastolic gallop were heard at the apex. There was marked congestion of the jugular veins with free systolic pulsation, and there was a pleural effusion on the right, and a large tender liver. The leucocyte count was 21,800/cu. mm. with 51 per cent eosinophils. Fig. 1 shows right axis deviation, slightly depressed S–T segments in leads II and III and low T waves. Circulation time from arm to tongue (5 ml. decholin) was 22 seconds. Injections of neoarsphenamine g. 0·45 afforded no relief. He was digitalized but without effect on the cardiac failure and on August 22, because the size of the heart was increasing, pericardial aspiration was attempted, but a small amount of fresh blood only was withdrawn. His condition was deteriorating, but very slowly, and the blood pressure fell to 95/80 with pulsus alternans. He was given injections of neptal with good results and was discharged in October, 1945. He remained in chronic congestive failure for the next year and died in November, 1946.

Necropsy. The body of a well-nourished man with cyanosis of the extremities and œdema of the legs.

Respiratory system: 300 ml. of yellowish fluid were in each pleural cavity. There were fairly dense adhesions over both lungs and between pleura and pericardium. The lungs were œdematous and showed patchy collapse. The pulmonary arteries were dilated and prominent and were flecked with atheroma.

Heart. There was a slight excess of clear fluid in the pericardium and numerous petechial hæmorrhages over the heart. The right auricle and ventricle and the left auricle were greatly dilated, and the left ventricle slightly so. Endocardial fibrosis at apex of the hypertrophied right ventricle extended into the papillary muscles. Organizing fibrous tissue caused adherence of the septal end of the tricuspid valve to the ventricular wall. The lower two-thirds of the left ventricular cavity were lined with fibrous tissue. The marginal cusp of the mitral valve was slightly adherent to the ventricular wall. There was moderate atheroma of the right and slight atheroma of the left coronary arteries. Other vessels were healthy.

Abdomen. Several pints of brownish ascitic fluid were present. There was severe chronic heart failure change in the liver with some fibrosis. Spleen was enlarged and congested and there was œdema and fibrosis of the pancreas. A recent infarct was present in the left kidney, and a calcified tuberculous gland was found at the ileocæcal junction.

Microscopy. Heart. Normal pericardium, with healthy coronary vessels. There is a mild diffuse interstitial fibrosis of the myocardium with patchy scarring which is confined almost entirely to the papillary muscles and to the myocardium immediately below the endocardium. The thebesian veins are dilated and contain loose connective tissue in which numerous thin-walled vessels and some iron-containing pigment are found. The endocardium is greatly thickened by old dense hyaline fibrous tissue and some areas of

loose connective tissue which like the thebesian veins contain thin-walled blood vessels and iron pigment. There are only a few peri-vascular leucocytes in the endocardium and no evidence of any active necrosis or inflammation. The endocardial fibrous tissue is covered by an intact endothelium and there is no mural thrombus (see Fig. 2).

Liver, passive venous congestion with early cardiac cirrhosis. Kidneys, small white infarct with arterial thrombus. Lung, congested; alveoli contain heart failure cells; small branches of pulmonary arteries contain ante-mortem thrombi. Spleen, voluntary muscle, intestine, and pituitary show no significant changes.

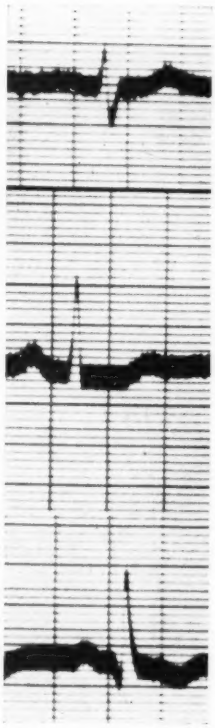

FIG. 1

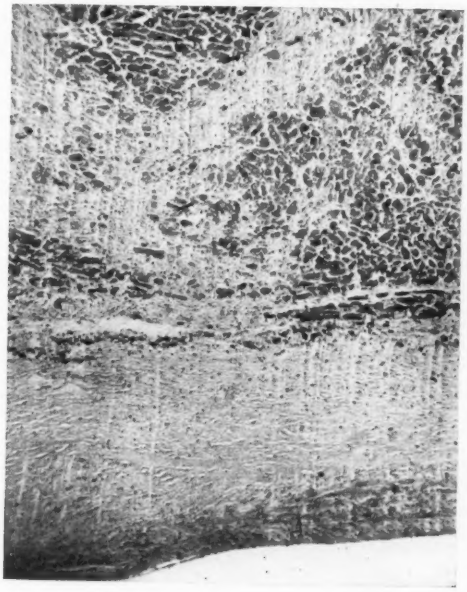

FIG. 2

FIG. 1.—Case 1. Sinus rhythm. Right axis deviation. T wave inverted in lead III. S–T segment slightly depressed in lead II.

FIG. 2.—Case 1. Low-power view of endocardium and underlying myocardium of left ventricle. Endothelium is intact. There is fibrous thickening of endocardium. There is considerable post-necrotic scarring of the underlying muscle.

Case 2. A district magistrate, aged 36, who had lived in Nigeria since 1946. There was no history of serious illness and his health while in Africa was excellent except for some lumps on the arms which appeared for a few days during summer, 1949, attributed to loa-loa. He first felt unwell in December, 1949, with fatigue, low fever and sweating, symptoms which were unaffected by anti-malarial therapy. He sailed for England in January, 1950, and on arrival still felt out of sorts. He was seen by a doctor on January 29, when he had a normal temperature and a pulse rate of 120; heart sounds were distant and rhonchi were heard throughout the chest. He was admitted to hospital and examination revealed an enlarged liver, and an exudate and several hæmorrhages in the left fundus. He complained of severe headache and

developed exaggerated reflexes with extensor plantar responses and bilateral ankle clonus. Blood smears were repeatedly negative for malarial parasites and lumbar puncture showed a high pressure (over 300 mm. water) and slightly raised protein (45 mg. per 100 ml.) in the spinal fluid. No trypanosomes were seen in the spinal fluid or in fluid aspirated from an enlarged cervical gland. The temperature rose to 102° F. and he became drowsy, irrational and incontinent. He was transferred on February 16, to the Hospital for Nervous Diseases, Queen Square, with an established spastic tetraplegia. The fundi were normal, heart sounds were distant and congestive failure was present. There was a leucocytosis (13,100/cu.mm.) with an eosinophilia of 18 per cent. On February 23, the Wassermann and Kahn reactions were positive. Neurological signs gradually diminished and the mental state improved but congestive failure increased. He was transferred to University College Hospital on March 29.

On examination: T. 99·4°; P. 120 (regular); R. 28; B.P. 110/80. Cyanosed with sluggish peripheral circulation, and venous congestion up to the ears with very free systolic pulsation. Congestive cardiac failure with considerable œdema, ascites, and pleural effusions. Heart enlarged, left border 15 cm. to left in 5th space and right border 4 cm. to the right. Apex beat could scarcely be felt. A protodiastolic gallop was heard shortly after admission and persisted thereafter. There were no murmurs. Signs of spastic tetraplegia were disappearing.

He was treated with digitalis, a low-salt diet and restricted fluids. Mercurial diuretics were exhibited as long as they were effective. Wassermann reaction was negative on March 29. Fig. 3 shows normal rhythm with right axis deviation and normal conduction, low-voltage complexes in all leads, flat T1 and T2, inverted T3 and slight depression of S–T in lead II. X-ray showed an enlarged heart with bilateral pleural effusions. E.S.R. was 16 mm. in 1 hour.

Thiamine chloride 20 mg. was given intramuscularly daily for 32 days. Mercurial diuretics ceased to be effective after four injections. Slow improvement occurred for 4 weeks. After this his mental state began to deteriorate, venous congestion increased and the peripheral circulation became gradually more sluggish. On May 6 he collapsed and became very breathless and cyanosed. Pulmonary embolism was suspected, and he died a few hours later.

Necropsy (Dr. J. D. Judah). The well-developed body of a young man. There was pitting œdema of the legs and the abdomen was distended. Both pleural cavities contained large amounts of turbid fluid. Pleural surfaces were normal.

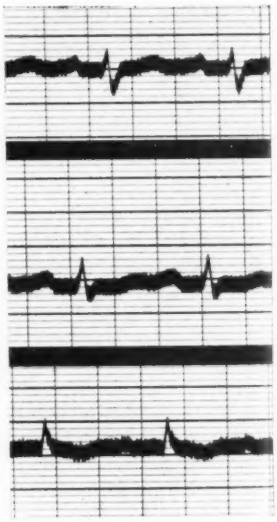

FIG. 3.—Case 2. Sinus rhythm. Low-voltage curves with right axis deviation. T waves low in all leads, inverted in lead III.

Lungs: R. 670 g; L. 370 g. The right lung contained several small ante-mortem thrombi in smaller vessels. There was no actual infarction. There were no thrombi or emboli in the left lung. There was no pulmonary œdema or bronchopneumonia, and no atheroma of the pulmonary vessels.

Heart: 600 g. The heart was greatly enlarged and there was some yellow turbid fluid in the pericardial sac, but no pericarditis. The cavities of both ventricles were almost filled with tough organizing thrombus firmly bound down to the endocardium (Fig. 4). In the right ventricle thrombus almost reached the tricuspid valve leaving a very small effective ventricular cavity. On the left thrombosis was rather less extensive covering only the apical and septal portions of the ventricular wall. The auricles were free of thrombus but the right auricle was enlarged and hypertrophied so that the auricular appendage was reduced to a slit. The valves were normal except for fenestration of one cusp of the aortic valve. The great vessels were normal without any sign of atheroma or syphilis. The coronary vessels and their branches were dissected out and showed no sign of atheroma or thrombosis. The cut surface of the ventricular wall showed advanced organization of the thrombus which was in places inseparable from the endocardium which was itself greatly thickened throughout the greater part of both ventricles. The inner half of the ventricular wall was whitish in colour with fibrous tissue spreading into it from the thick fibrous endocardium. Liver: 1820 g.; enlarged with a deep red and yellow mottled appearance. It was firm in texture and the portal and hepatic vessels were normal. Kidneys: normal macroscopically. Alimentary canal: there was a leash of dilated and engorged veins at the lower end of the œsophagus, but no other abnormality. There was about nine pints of ascitic fluid. Vessels: an antemortem thrombus was found

in the right femoral vein. Other vessels were normal. Brain: the brain was somewhat œdematous. The great vessels appeared normal, but there was great congestion of the veins. The gyri were somewhat flattened. Petechial hæmorrhages were scattered throughout the brain, and there were numerous small slightly pigmented scars. On the right side, the internal capsule and caudate nucleus were involved in a large area of softening of fairly recent origin.

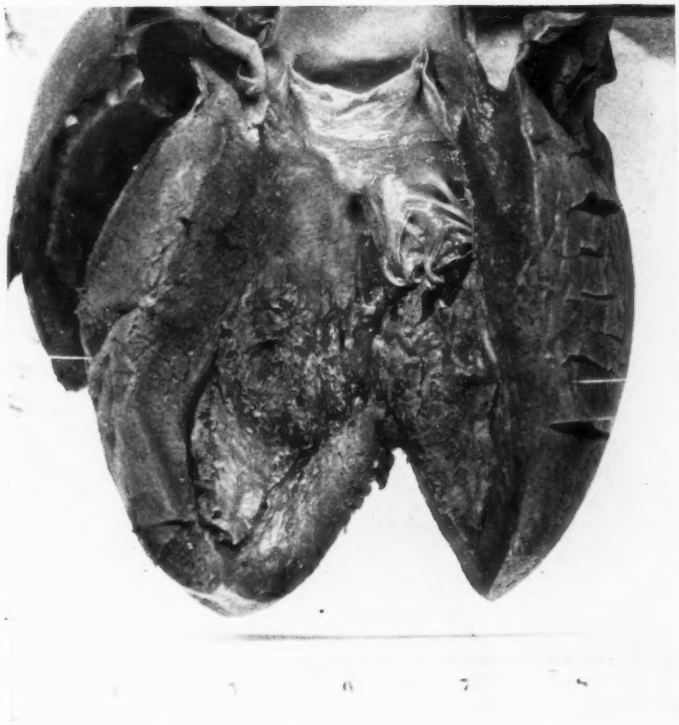

FIG. 4.—Case 2. Left ventricle opened to show extensive organizing thrombus filling the apex of the cavity.

Microscopy. Heart: pericardium normal; myocardium shows several post-necrotic fibrous scars from multiple emboli in the smaller coronary arteries and arterioles; these emboli are largely composed of platelets and fibrin and resemble the structure of the friable superficial parts of the endocardial thrombus. The intra-mural thebesian veins are distended and their lumina filled with loose connective tissue in which much iron-containing pigment and numerous capillaries are seen. Some of these capillaries are proliferating and many others show ectasia. These veins appear to have been obstructed, to have thrombosed, and to be partly recanalized, the young capillaries being stuffed with red cells suggesting that obstruction persists. The endocardium is grossly thickened, being made up of loose connective tissue in which small areas of dense collagen are found; much iron-containing pigment is present in these areas. Overlying the thickened endocardium is a deep layer of ante-mortem platelet and fibrin thrombus. Young capillaries and fibroblasts are growing into this clot (Fig. 5). Both right and left ventricles show these endocardial changes. Coronary arteries are normal apart from the emboli in their smaller branches.

Lungs: mucous bronchitis, patchy atelactasis. A few small branches of the pulmonary arteries contain blood-clot emboli. Liver: back pressure changes and early cardiac cirrhosis. Spleen and kidneys: several small emboli. Brain: arterioles of the brain contain several blood-clot emboli with small foci of cerebral

softening in which scavenger cells are found. Voluntary muscle: normal muscle fibres. Some perivascular and perimural aggregates of lymphocytes and polymorphonuclear leucocytes but no changes specific of polyarteritis nodosa.

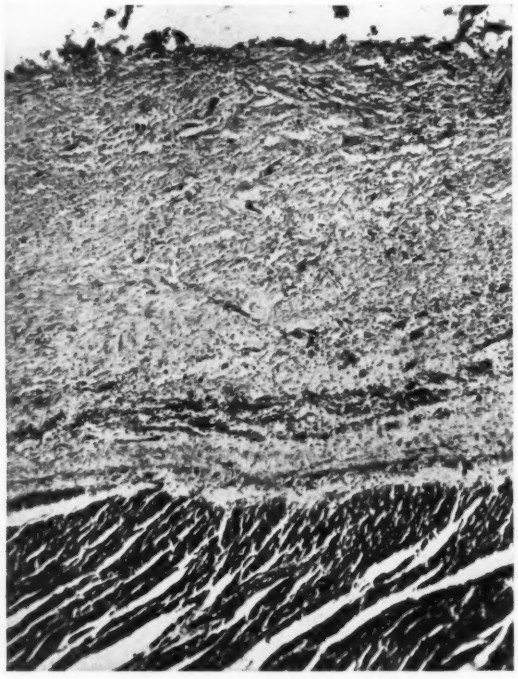

FIG. 5.—Case 2. Low-power view showing greatly thickened endocardium with loss of the endothelium. Underlying muscle is healthy.

DISCUSSION

The clinical picture of chronic congestive failure, regular pulse, low blood pressure, enlarged heart with gallop rhythm, and indefinite electrocardiographic changes could be found in any severe myocardial lesion. The absence of anginal pain is worth emphasis as it may help in distinguishing these cases clinically from coronary artery disease. The widespread small emboli found in the brain were undoubtedly the cause of the neurological findings in Case 2 and it was their multiplicity that made diagnosis difficult. Similar signs were found in the case of Edge (1946). They were attributed to the effect of arsenical therapy, but since the brain was not examined at necropsy proof of this was lacking, and the extensive mural thrombus in the left ventricle made an embolic lesion likely.

The eosinophilia could be attributed to loa-loa. It has, however, been described previously in endocardial fibrosis. Not only is it mentioned by Davies (1948) in his cases in East Africa but also in the Continental literature. The two cases of Loeffler (1936) had an eosinophilia of 70 per cent and that of Egger (1944) also had a high count. The remarkable case of Mumme (1940) may be mentioned where eosinophilia of 60 per cent was found and fibrosis of the endocardium occurred with fibroplastic inflammation of the aorta and thrombo-arteritis obliterans of the visceral

and cerebral vessels. Although eosinophilia might be disregarded in Africa where parasitic infestations are common, in Europe it is usually significant.

The lumps noticed on the arms were 2·5 to 7·5 cm. in diameter, itching but not painful, and lasted only a few days. Any such lesions occurring in West Africa are likely to be attributed to loa-loa. In these two cases there were no ocular symptoms and no microfilaria were found in the blood later on. It seems possible that these skin lesions had some significance in relation to the cardiac disease that developed later.

The essential lesion in both cases was an intense fibrosis of the subendothelial connective tissue of the endocardium. If this was the result of an inflammatory process no evidence of it remained. In Case 1 the endothelium was intact; the fibrosis extended into the myocardium along the thrombosed thebesian veins. There was also extensive fibrosis in the subendocardial muscle which appeared to have followed necrosis of muscle; here again there was no cellular reaction. This scarring of the subendocardial muscle seemed due to interference with its blood supply which is largely direct from the ventricular cavity. Post-necrotic scarring was much less marked in Case 2 but here patchy scarring from embolic obstruction of small coronary vessels was also found. In the second case the endocardial fibrosis was more extensive and the endothelium replaced by widespread organizing thrombus.

Ætiology

The cause of endocardial fibrosis is unknown. The insidious onset of the disease which probably long precedes the appearance of symptoms has made clinical study fruitless. The clinical and pathological resemblance of the cases occurring in Africa or in Africans to those found elsewhere does not imply that the cause is necessarily identical. Discussion is mainly concerned with those cases occurring in Africa. Malnutrition, including vitamin deficiencies, infection or parasitic infestation, and abnormal tissue response of the endocardium must be considered.

Davies (1948) working in East Africa concluded that malnutrition was the most likely cause. This was also the opinion of Smith and Furth (1943). In all Davies' cases evidence of malnutrition was found elsewhere in the body. Describing the native diet, he remarks that although very poor in protein it contains ample amounts of the B complex vitamins. Malnutrition is, however, very common amongst East African natives. The cases of Smith and Furth were regarded as a form of beri-beri as their diets were deficient in the B vitamins. The case of Toreson (1944) is described as being undernourished but no specific deficiencies are mentioned. In none of the other cases reported is malnutrition suggested. The West African soldiers described by Bedford and Konstam (1946) were probably having a fuller and better-balanced diet in the Army than they had ever had previously but it remains possible that the disease was established before they enlisted. Thiamin deficiency is the only dietary cause of cardiac disease that has yet been recognized. The cardiac effects of thiamin deficiency found clinically and experimentally must therefore be compared with endocardial fibrosis.

Although the cardiac form of beri-beri is seldom found in association with advanced peripheral neuritis, yet early neurological changes are common. The neurological changes sometimes found in endocardial fibrosis as in Case 2 bear no resemblance to peripheral neuritis. Clinical reports of cardiac beri-beri emphasize also that the condition of the circulation is very different from that described in endocardial fibrosis. There is a rapid bounding pulse with dilated vessels in the skin and increased pulse pressure, in fact, until the terminal stages, a failure of the high-output type. Recovery in the cardiac form of beri-beri following administration of thiamin is dramatic and almost invariable. Rapid improvement may be expected even in a moribund patient. Apart from true beri-beri, cardiac changes have been described in patients in America suffering from severe malnutrition with deficiency of the B vitamins. In a series of nine hundred such patients, Weiss and Wilkins (1936) found marked cardiovascular changes in a hundred and twenty, but in none of these did the condition resemble endocardial fibrosis. Pathologically, the lesion of beri-

beri is a hydropic degeneration of the muscle fibres: myocardial necrosis and fibrosis are not found and there is no change in the endocardium.

Experimental thiamin deficiency must be severe and prolonged for myocardial changes to appear. Cardiac failure has been brought about in animals fed on deficient diets with recovery on the administration of thiamin. A focal necrosis of the myocardium was produced which appeared to be reversible. Fibrotic lesions have been described only once and they were diffusely distributed throughout the myocardium. In chastek paralysis, a disease of foxes believed to be due to a deficiency of thiamin, there is occasionally extensive myocardial necrosis and fibrosis (Evans *et al.*, 1942).

Comparison with beri-beri and experimental thiamin deficiency gives no grounds for believing that endocardial fibrosis is due to deficiency of the B vitamins. The diet of the African is low in protein and high in carbohydrate. The relationship of such a diet to fatty degeneration and fibrosis of the liver is known but no cardiac changes have been reported in man or in experimental animals with hepatic disease of dietary cause. The occurrence of endocardial fibrosis in two well-nourished Europeans provides further evidence against the disease being due to dietary deficiency.

Various lesions in the myocardium and endocardium have been attributed to syphilis (Brooks, 1913; Morris, 1937). As well as gummata, patchy necrosis and cellular infiltration of the myocardium, and endocardial thickening have been thought syphilitic. Warthin (1925) described a series of eight cases in which extensive syphilitic lesions were present throughout the body where a diffuse inflammation with patchy fibrosis of the myocardium were found. Spirochætes were demonstrated in these lesions by special methods. Other pathologists have failed to confirm this, but Magill (1935) describes five cases of cardiac failure with histories of syphilis and positive serological reactions in which scattered round cell infiltrations and scarring of the myocardium were present. It is unwise, however, to diagnose syphilitic myocarditis when signs of syphilis are lacking elsewhere and when the cardiac lesions are not gummatous. No cases of endocardial fibrosis have been definitely attributed to syphilis, but in several of Davies' (1948) cases a positive Wassermann reaction was found. This could be attributed to yaws, but evidence of syphilis elsewhere was occasionally found. The patient described by Edge (1946) was undergoing antisyphilitic treatment when the illness began. In Case 2 a positive serology was found which later became negative; there was, however, no history and no clinical or pathological evidence of syphilis. The absence of syphilitic lesions elsewhere in the great majority of reported cases, the rarity of positive complement fixation tests, and the pathology of the lesion oppose a syphilitic ætiology.

The possibility of cardiac lesions being caused by African trypanosomiasis must be examined as there is no doubt that in the acute form of American trypanosomiasis or Chagas' disease the myocardium is involved as trypanosomes may be demonstrated inside muscle fibres. Chagas' disease has also a chronic form, in which the diagnosis is established by indirect means, which appears common in endemic areas. A form of myocardial fibrosis with cardiac failure is common in South America and a positive complement fixation test for *T. Cruzi* is found in such cases. The occurrence of myocarditis in the acute form of the disease and the recognition of a chronic myocarditis in the endemic regions has led to the identification of chronic myocarditis in South America with Chagas' disease. The circumstantial evidence for this is strong and a recent review of seventy-three cases of the chronic myocarditis of Chagas' disease (Ponde, 1948) describes a positive complement fixation test in every case and a positive zenodiagnostic test in thirteen of them, and in one out of four necropsies the trypanosome was demonstrated in the myocardium. Disorders of rhythm are very frequent in this type of chronic myocarditis (Chagas, 1928; Ponde, 1948). In this it differs clinically from endocardial fibrosis. Pathologically, there is patchy degeneration of myocardium, infiltration with inflammatory cells, and fibrosis (Johnson, 1943; Chagas, 1928; Ponde, 1948). The changes differ from those of endocardial fibrosis in being distributed throughout the entire thickness of the myocardium and there is no endocardial thickening or mural thrombosis. Comparison with the chronic myocarditis attributed to South

American trypanosomiasis gives no grounds therefore for suspecting infection with this type of organism.

Trichina spiralis is recognized as causing a myocarditis that may prove fatal in the acute stages of trichiniasis (Zoller, 1927). There is necrosis of muscle fibres with eosinophilic infiltration and the larvæ may be found in the heart. There is no evidence that chronic heart disease follows such an invasion and in any case it is likely that the larvae would be demonstrable in the heart or elsewhere.

Diphtheritic myocarditis occasionally leads to a patchy fibrosis in the myocardium, and it has been suggested that this could lead to cardiac failure in later years. A history of severe diphtheria has not been found in cases of endocardial fibrosis and it is unlikely that such an illness could pass unnoticed. Furthermore the lesion in diphtheritic myocarditis is widespread and the endocardium is not involved.

Cases of scleroderma have been described in which myocardial fibrosis has developed with intractable heart failure (Weiss *et al.*, 1943). The clinical course and electrocardiographic changes resembled those of endocardial fibrosis but severe scleroderma was present for a long period before cardiac symptoms appeared. The heart in such cases showed a fibrotic change throughout the whole myocardium and the endocardium was not particularly affected. Scleroderma affecting the skin or the other viscera has not been described in cases of endocardial fibrosis. A resemblance of the lesions to those of scleroderma and certain cases of disseminated lupus erythematosus must, however, raise the possibility of endocardial fibrosis falling into the ill-defined category of the collagen diseases.

The frequency of eosinophilia may suggest that the nature of the disease lies in some allergic or hypersensitivity reaction. This was submitted by Mumme (1940) in discussing his case where endocardial fibrosis was found in association with intimal changes in many vessels throughout the body resembling those of thromboangiitis obliterans. There is no clinical or pathological evidence to support such a suggestion and in none of the experiments conducted with artificially induced hypersensitivity have endocardial lesions of this type been produced.

The relatively high incidence of endocardial fibrosis in Africa and the susceptibility of well-nourished Europeans favour an infectious cause in the African cases, and it is possible that sporadic cases encountered elsewhere are caused by some entirely different agent. The frequency of eosinophilia suggests an unrecognized parasitic infection or possibly some allergic response of the body. The lesion itself does not appear inflammatory but could be the result of the healing of an inflammatory process as in the fibrous scarring that follows rheumatic valvulitis. Early diagnosis of the condition must remain difficult except possibly in Africa but it is only from study of cases in their early stages that a causative organism is likely to be identified, and it is only in the early stages that therapeutic measures are likely to be of any use.

Summary

Attention is drawn to endocardial fibrosis as a cause of chronic congestive failure frequently complicated by multiple arterial emboli.

The clinical and pathological features of this condition are described.

The greater frequency of this disease in Africa than in Europe or America is stressed and two fatal cases described occurring in Europeans who had been living in West Africa.

The cause of endocardial fibrosis is discussed and vitamin B deficiency rejected. No other nutritional cause of cardiac disease is recognized.

Possible infections are discussed and it is considered possible that an unrecognized parasitic, bacterial, or viral agent may cause the disease.

I wish to thank Dr. Evan Jones for his permission to publish Case 1 and for allowing me access to his records at St. Thomas' Hospital, and Prof. M. L. Rosenheim for permission to publish Case 2. My thanks are also due to Dr. R. A. B. Drury for his great assistance with the pathology and to Dr. D. Evan Bedford and Dr. J. D. N. Nabarro for their advice and help, and to Mr. A. Bligh who prepared the photographs.

References

Bedford, D. Evan, and Konstam, G. L. S. (1946). *Brit. Heart J.*, **8**, 236.
Boikan, W. S. (1931). *Virchow's Arch. path. Anat.*, **282**, 46.
Brooks, H. (1913). *Amer. J. med. Sci.*, **146**, 513.
Chagas, Ev. (1928). *Arch. Mal Coeur*, **21**, 641.
Davies, J. N. P. (1948). M.D. thesis, Bristol.
Edge, J. R. (1946). *Lancet*, **2**, 675.
Egger, P. (1944). *Schweiz. Z. Path. Bakt.*, **7**, 237.
Evans, C. A., Carlson, W. E., and Green, R. G. (1942). *Amer. J. Path.*, **18**, 79.
Flynn, J. E., Mann, F. D. (1946). *Amer. Heart J.*, **31**, 757.
Gallavardin, L., and Gravier, L. (1929). *Arch. Mal. Coeur*, **22**, 379.
Johnson, C. M. (1943). *Med. Clin. North America*, 822.
Josserand, E., and Gallavardin, L. (1901). *Arch. Gen. Med.*, **188**, 513.
Kugel, M. A., and Stoloff, E. G. (1933). *Amer. J. Dis. Child.*, **45**, 828.
Levy, R. L., and Rousselot, L. M. (1933). *Amer. Heart J.*, **9**, 178.
Loeffler, W. (1936). *Schweiz. med. Wchnschr.*, **17**, 817.
Magill, T. P. (1935). *Bull. Johns Hopkins Hosp.*, **57**, 22.
Mahon, C. S. (1936). *Amer. Heart J.*, **12**, 608.
Morris, J. C. (1937). *J. Amer. med Assoc.*, **108**, 169.
Mumme, C. (1940). *Z. klin. Med.*, **138**, 22.
Ponde, A. (1948). *Prensa Med. Argent.*, **35**, (i), 1075.
Reisinger, J. A., and Blumenthal, B. (1941). *Amer. Heart J.*, **22**, 811.
Roque, G., and Levy, L. (1914). *Arch. Mal. Coeur*, **7**, 10.
Smith, F. M., and Stephens, R. L. (1938). *Trans. Ass. Amer. Phys.*, **53**, 120.
Smith, J. J., and Furth, J. (1943). *Arch. intern. Med.*, **71**, 602.
Toreson, W. E. (1944). *Ibid.*, **73**, 375.
Ware, E. R., and Chapman, B. M. (1947). *Amer. Heart J.*, **33**, 530.
Warthin, A. S. (1925). *Ibid.*, **1**, 1.
Weiss, S., and Wilkins, R. W. (1936). *Ann. intern. Med.*, **11**, 104.
——, Stead, E. A., Warren, J. V., and Bailey, O. T. (1943). *Ibid.*, **71**, 749.
Zoller, H. (1927). *Virchows Arch. path. Anat.*, **2665**, 430.

A COMPLICATION FOLLOWING CORONARY SINUS AND CARDIAC VEIN CATHETERIZATION IN MAN

BY

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Right auricular catheterization in man is a safe and simple procedure, but the introduction of the catheter into the right ventricle and pulmonary artery is often technically more difficult and introduces new risks. Most of these can be avoided if their existence is recognized. The unrecognized entry of the catheter into a cardiac vein either via the coronary sinus or even directly from the right atrium constitutes one of these risks. In a total of approximately 300 right heart catheterizations at this hospital during the past two years, in which the prime object was to enter the right ventricle or pulmonary artery, there have been five such complications. A preliminary report on three of these cases, tentatively labelled " coronary thrombosis " has already been made by Zimdahl (1951). In all cases Cournand catheters were passed through the median basilic vein and directed under fluoroscopic control. A continuous slow infusion of heparanized 5 per cent glucose was maintained through the catheter.

Case Reports

Case 1. A 69-year-old woman, suffering from chronic bronchitis and emphysema was catheterized for assessment of her cardiac condition. No pre-medication was given. A size 9F catheter was used. After leaving the right atrium the catheter was seen in the antero-posterior view to pass diagonally across the heart to " the pulmonary outflow tract." Four unsuccessful attempts were made in this position to advance the tip further into the pulmonary artery, but each time the tip advanced diagonally and was arrested at the left border of the cardiac silhouette. The patient later admitted that she had had substernal pain going through to the back in the interscapular region at this time. Pressure recordings were low and a blood sample aspirated appeared to have a very low oxygen saturation on immediate inspection. It was then suspected that the catheter was in the coronary sinus and this was confirmed on turning the patient into the left oblique position where the catheter was seen to be lying at the posterior border of the heart. The patient now complained for the first time of pain and exhaustion. The catheter was withdrawn. She became cold and cyanosed, sweated profusely, and nausea was soon followed by vomiting. The pulse became feeble, the systolic blood pressure being 80 mm., but the rate was unchanged at 80–90 a minute. The jugular venous pressure rose slightly to 2 cm. above the sternal angle. She was immediately returned to the ward where she was given morphia and oxygen therapy and slow digitalization was begun. An electrocardiogram a few hours later showed no significant change since admission.

Over the next five days she gradually improved, the blood pressure rising to 120/70 mm. after twenty-four hours. The pain persisted for five days, although gradually diminishing in intensity. Referred pain in the back was a predominant feature in this case. During the first three days a transient pyrexia up to 100° F. was seen. On the fifth day the patient was found to have auricular fibrillation and this rhythm change persisted for twenty-four hours, after which sinus rhythm returned. The erythrocyte sedimentation rate rose during the first week to 27 mm. in one hour (Westergren), returning to normal after a further week. There was no significant change in total white cell count.

Serial electrocardiograms during the first five days (Fig. 1) showed progressive changes with S–T elevation and T wave inversion in V5, VF, and III without pathological Q waves. These were interpreted as indicating

postero-lateral myocardial ischæmia. Recovery was complete by the tenth day, but the patient was left with persistent tinnitus and giddiness, probably due to the prolonged low blood-pressure state.

Case 2. A 59-year-old woman, suffering from pulmonary fibrosis of obscure ætiology, was catheterized for further assessment of a difficult diagnostic problem. She was given 3 grains of sodium amytal orally as premedication. The catheter was introduced easily and passed from the right atrium " to the pulmonary outflow tract." On reaching the left border of the cardiac silhouette in this position, the tip was seen to curve downwards again for a short distance. Screening in the antero-posterior position only was used to locate the catheter. The patient then complained of pain in the back between the shoulder blades and was noticed to have a cardiac irregularity. The catheter was at once withdrawn and 100 mg. of procaine hydrochloride in 1 per cent solution given intravenously. Her condition now gave cause for alarm. The peripheral pulse was unobtainable, but the apical rate was 80 and regular. She was cold and cyanosed and unable to comprehend and answer questions. On return to the ward continuous oxygen was given by BLB mask

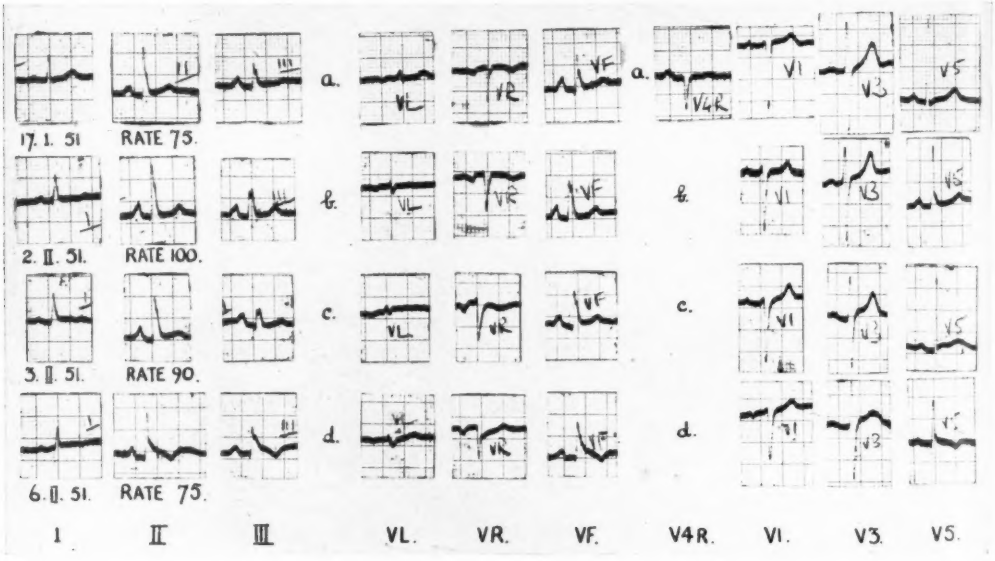

FIG. 1.—Case 1. (a) Control cardiogram before catheterization. (b) 2 hours after catheterization. No change beyond increase in heart rate and flat T wave in I, VL. (c) Slight S–T segment elevation and flattening of T wave in II, VF, V5. (d) Marked S–T segment elevation in II, III, VF, V3, V5 with T. wave inversion in II, III, VF, V5. Postero-lateral myocardial ischæmia.

and her condition improved after twenty minutes sufficiently to enable her to speak, when she complained of persistence of interscapular and sternal pain without radiation elsewhere.

Routine treatment for shock was given, and in view of vomiting a rectal glucose drip was set up. The following day her blood pressure level had improved, rising to 100/70 mm. The pulse remained of normal rate and regular. The jugular venous pressure was now noted to have risen to 2 cm. above the sternal angle. There was also a slight rise in temperature to 99·5° F., which persisted for five days.

Electrocardiograms (Fig. 2) were taken three hours after catheterization and also three days later. The first tracing showed no change beyond a decrease in voltage but the second gave evidence of pericarditis.

The patient continued to complain of interscapular and sternal pain at this time, but no pericardial rub or evidence of pericardial effusion was detected, although signs of these were constantly sought for. The subsequent course in this patient was uneventful and recovery was complete by the tenth day.

Case 3. A 66-year-old man, suffering from Paget's disease, with some question of ischæmic heart disease, was catheterized. No premedication was given. The patient appeared quiet and not apprehensive. After entering the right atrium attempts were made to advance the catheter into the right ventricle but

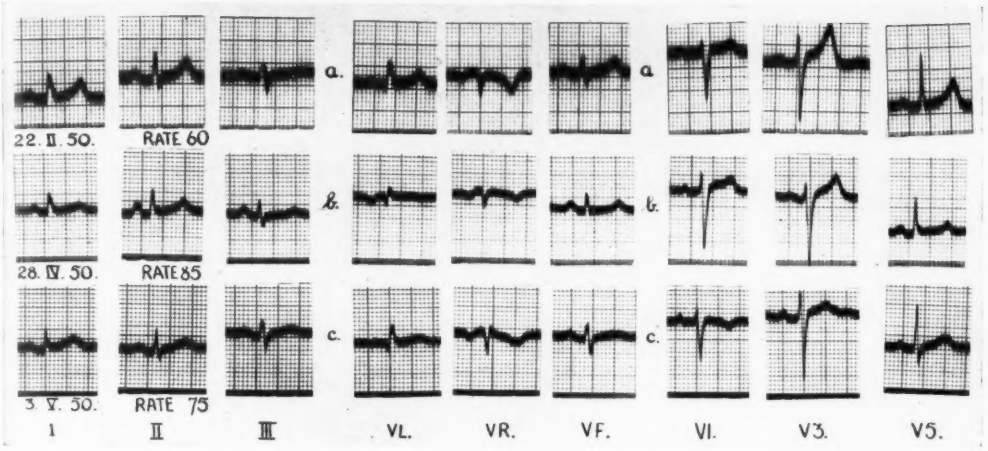

FIG. 2.—Case 2. (a) Control cardiogram before catheterization. (b) 1 hour after catheterization. No change beyond low voltage and slight increase in heart rate. (c) Slight S–T segment elevation and coving in I, II, III, V3, V5 with T wave inversion in V1; suggestive of pericarditis.

each time this manœuvre was attempted the catheter was seen in the antero-posterior view to be passing into the coronary sinus. Once on reaching the left border of the cardiac shadow the tip of the catheter curved downwards for a short distance, an event exactly parallel what was seen in Case 2. The patient at once complained of pain in the chest, substernal radiating through to the back and up to the back of the neck into the ears and occiput. It was noted at this time that the pulse was irregular and the catheter was immediately withdrawn. Following this the pain persisted, but the pulse became regular again, remaining at a normal rate of 80–90 a minute. The sequence of events during the next three hours was complicated by the development of a rigor.

No major fall of blood pressure occurred at any time in this case and there was no nausea nor vomiting. He was free from pain when lying still in bed on the following day, but complained of mild upper sternal pain when up in the ward. The temperature was raised to 99° F. for three days. The electrocardiogram showed no significant change. Recovery was complete by the third day.

Case 4. A 54-year-old woman suffering from benign hypertension was catheterized for study of the haemodynamic effects of hexamethonium therapy. No premedication was given. A size 7F catheter was used. After leaving the right atrium the catheter appeared to pass easily into the lower portion of the right ventricle, its course running parallel and close to the inferior border of the cardiac silhouette as seen in the antero-posterior position. On reaching the apex of the heart the tip curved upwards for a short distance. The patient then complained of slight substernal discomfort and the catheter was withdrawn about five centimetres. The pain going off, the catheter was again advanced. The pressure was now measured and found to be low. It was therefore suspected that the catheter lay in the coronary sinus and an attempt was made to withdraw a blood sample to confirm this. A few ml. of slightly blood-stained fluid were withdrawn and similar amounts came back into the syringe on repeated aspirations. In view of this finding it was considered that the catheter had possibly perforated a vein and lay not in the coronary sinus but in the pericardium into which fluid had been flowing from the manometer reservoir. The catheter was now withdrawn and the patient began to complain of increasing substernal pain radiating to the neck and jaws. The pulse did not rise, remaining at 80–90 a minute, but the blood pressure fell immediately from 190/110 to 110/70 mm. There was no nausea and no peripheral signs of collapse.

On return to the ward the patient's general condition was quite good. The jugular venous pressure was found to be 1 cm. above the sternal angle. There were no clinical signs of pericarditis and a cardiogram taken immediately was normal as was a chest X-ray the following day. The pain persisted for three days, gradually diminishing. The blood pressure returned to 150/85 mm. after twenty-four hours. Serial cardiograms during the next three days showed no significant change and the temperature, total white cell

count, and erythrocyte sedimentation rate did not rise. Recovery was complete by the third day except for transient slight attacks of præcordial pain during the next two weeks.

The exact course of the catheter in this case remains in doubt. It is probable that it entered the pericardium through a cardiac vein. Its course, as watched in the antero-posterior position, closely followed the direction of two cardiac veins, the middle cardiac vein, catheterization of which has been reported by Bing *et al.* (1947) and the right marginal vein, which may either drain directly into the right atrium or into the coronary sinus via the lesser cardiac vein. It seems possible therefore that retrograde catheterization of one of these veins, either directly from the atrium or via the coronary sinus, led to its perforation. The choice of a relatively small bore catheter (size 7F) in this case may have facilitated this manœuvre.

Case 5. A 48-year-old man, suffering from rheumatic heart disease with mitral stenosis, auricular fibrillation, and congestive cardiac failure, was catheterized on two successive occasions for hæmodynamic assessment of progress. The first catheterization was carried out without incident. The notes referring to the second catheterization are incomplete, but the main facts are outlined here. The passage of the catheter from the right atrium into the right ventricle and pulmonary artery was viewed in the antero-posterior position. After advancing the catheter into " the pulmonary artery " pressures were measured but no free reading could be obtained, and it was apparent that the coronary sinus had been entered. The catheter was withdrawn into the atrium and was finally passed successfully into the right ventricle where satisfactory pressure recordings were made. Shortly afterwards the patient began to complain of sternal pain, became cold, pale and collapsed, and the blood pressure was found to have fallen from 120/80 to 90/60 mm. The pulse remained regular at 90 a minute. The investigation had therefore to be terminated and the patient was returned to the ward, where he was given oxygen therapy and routine treatment for shock.

During the next week the patient continued to have right sternal pain intermittently and on the fourth day after catheterization developed a pericardial rub. Serial cardiograms showed changing patterns in the left chest leads with development of an RSR pattern with S–T elevation in leads V4 and V5. This change was maximal on the fifth and sixth days after catheterization, reverting later to a more normal RS pattern in V5, but with T wave inversion in V3 and V5. These cardiographic findings were considered compatible with a small antero-lateral myocardial infarct. Over this period the patient had an intermittent low pyrexia, the erythrocyte sedimentation rate rose to 32 mm. in one hour (Westergren), but the white cell count was not raised. Recovery was complete after a fortnight and there have been no sequelæ.

Discussion

The position generally occupied by the catheter is shown diagrammatically in Fig. 3. The clinical picture in all five cases, while varying in the degree of severity, was essentially similar in nature. Substernal pain radiating to the back, coming on at once during cardiac catheterization, was a characteristic of the three cases in which there was good evidence on screening that a cardiac vein had been entered via the coronary sinus. In the fourth case, in which the pericardium was probably entered via a cardiac vein, the site of radiation of substernal pain was different in that it spread to the neck and jaws only and not to the back. In the fifth case, a detailed account of events during catheterization and of exact symptomatology is lacking, but the general course of events strongly suggests that it should be included in the group. The severity of the initial collapse and degree of fall in blood pressure corresponded with the subsequent duration of substernal pain and the time elapsing before recovery.

The pathological process responsible for these clinical changes is uncertain, since, happily, all patients made a good recovery. Bing *et al.* (1949) reported no complications in studies with coronary sinus catheterization in man, but in his work care was taken not to advance too far into the coronary sinus. No strict parallel can be drawn between the experimental work of Gross *et al.* (1936) and the surgical approach to angina pectoris of Fauteux (1946), in which the coronary sinus was ligated, since the catheter is not of sufficient diameter to obstruct the mouth of the coronary sinus. It is of interest, however, to note that bradycardia following coronary sinus ligation was a constant finding in Gross's experiments, in view of the absence of any marked increase in pulse rate in the presence of a profound fall in blood pressure seen in our cases. It is probable that cardiac vein rather than coronary sinus catheterization is the harmful procedure, as in all our cases the catheter was passed to the point where it became wedged in the vein and could not be advanced

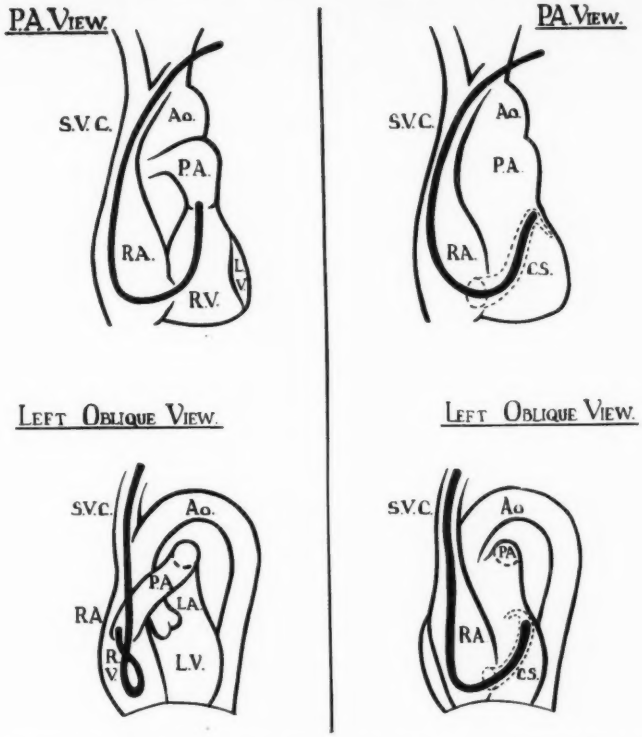

FIG. 3.—Diagram to show fluoroscopic appearances of a cardiac catheter in the pulmonary outflow tract and in the coronary sinus. On the left the catheter is seen in the right atrium and right ventricle with the tip in the pulmonary outflow tract. On the right the catheter is seen in the right atrium and coronary sinus with the tip at the origin of the coronary sinus.

further. Our experience of this unfortunate complication is not unique, as Dr. Warren Smith of New York has kindly informed us of a similar incident.

Goodale *et al.* (1948) in experiments on dogs, in which deep coronary catheterization was practised, reported hæmorrhages in the myocardium and coronary vein thromboses. Electrocardiographic changes were also noted by him in experiments in which the catheter was inserted into the great cardiac vein, with the development of T wave inversion and S–T segment elevation in one or more standard leads following the procedure. Such changes were associated at subsequent necropsy with intramural sub-epicardial hæmorrhage in areas drained by the catheterized vein in one case and in another with thrombotic occlusion of the great cardiac vein. No electrocardiographic changes were noted following experiments in which the catheter was inserted only a short distance into the coronary sinus. It is possible that a similar pathological process occurred in our cases, due to blocking of blood flow and damage to a cardiac vein with resultant myocardial injury in the area of muscle drained by this vein. The cardiographic changes suggesting localized myocardial ischæmia in two cases and pericarditis in a third lend support to this theory. A pericardial rub developed in one and in Case 4 there was strong evidence that the pericardium was entered by the catheter, but in none was there evidence of cardiac tamponade or pericardial effusion. It is worthy of note that four of our patients were of a type or age liable to have pathological changes in the coronary arteries.

It is suggested that the complication described in this paper can be avoided if due precautions are taken during the passage of the catheter from the right atrium to the right ventricle using fluoroscopic control. It has been shown by Hellerstein *et al.* (1951) that the anatomical variations of the orifice of the coronary sinus are great and in view of this it is probably unwise to attempt to recognize a typical course, in the antero-posterior view, of a catheter entering the coronary sinus. Screening in the left oblique position (Fig. 3) removes any possible doubt as to whether the catheter is entering the coronary sinus or the right ventricle, and we have now adopted this procedure in every case as a precaution against a recurrence of this serious complication.

Summary

Inadvertent coronary sinus and cardiac vein catheterization in subjects past middle age has been followed by præcordial pain and collapse in five patients: all of them made a good recovery.

In one case there was evidence that a vein was perforated.

Electrocardiograms in three cases showed changes compatible with myocardial ischæmia or pericarditis.

It is important to realize the possible serious consequences of coronary sinus and cardiac vein catheterization and recommendations are made for the avoidance of this complication.

References

Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. H., and Kety, S. S. (1949). *Amer. Heart J.*, **38**, 1.

——, Vandam, L. D., Gregoire, F., Handelsman, J. C., Goodale, W. T., and Eckenhoff, J. E. (1947). *Proc. Soc. Exp. Biol. Med.*, **66**, 239.

Fauteux, M. (1946). *Ann. Surg.*, **124**, 1041.

Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G. (1948). *Amer. J. Physiol.*, **152**, 340.

Gross, L., Silverman, G., and Master, A. M. (1936). *Amer. Heart J.*, **11**, 734.

Hellerstein, H. K., and Orbison, J. L., (1951). *Circulation*, **3**, 514.

Smith, Warren, W. (1951). Personal communication.

Zimdahl, W. T. (1951). *Amer. Heart J.*, **41**, 204.

CASE REPORTS

BILATERAL SUPERIOR VENÆ CAVÆ ACCOMPANIED BY PATENT DUCTUS ARTERIOSUS

BY

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From the Children's Hospital, Birmingham

The most common congenital anomaly of the veins is a persistent left superior vena cava (Abbott, 1933), but the condition has only rarely been diagnosed during life. Abbott collected 36 examples of the condition, all recognized for the first time post mortem. Of these no less than 27 were associated with other deformities such as septal defects, pulmonary stenosis, and the entry of pulmonary veins into the left superior vena cava.

In 1939 Chouke was able to collect 205 reported cases, and in the eleven years since his paper was published a further 7 cases have been described (Prows, 1943; Dohn, 1944; Lam, 1945; Campbell and Hills, 1950; Dean, 1950). It was not until 1945 that the condition was diagnosed during life when Lam observed a persistent left-sided superior vena cava whilst he was operating on a patent ductus arteriosus. In the past three years, at the Birmingham Children's Hospital, a persistent left superior vena cava has been encountered in 4 of 14 cases undergoing surgical treatment for pulmonary stenosis, but it has not been seen in any of the 65 patients operated on for patent ductus arteriosus.

The introduction of such diagnostic methods as angiocardiography and right heart catheterization has resulted in the pre-operative recognition of the anomaly on several occasions (Campbell and Hills, 1950; Dean, 1950) and a further example of this will now be described.

Case Report

A one-year-old girl was referred to the out-patients department because of a cardiac murmur. She had always been well. She was small but active, with no cyanosis, no clubbing of the fingers, and no distension of jugular veins. The pulse was regular, equal in both wrists and collapsing, the blood pressure being 110/50. Pulsations in the femoral arteries were normal. There was a slight precordial bulge. The apex beat was not well localized but could be felt to the left of the sternum in the fourth space. A loud systolic murmur, accompanied by a thrill, could be heard all over the precordium but was loudest in the second left intercostal space near the sternum. In this area there was also an early diastolic murmur. No other abnormal physical signs were found.

Investigations. A blood count showed no essential abnormalities. Fluoroscopic examination showed enlargement of the heart, especially to the right of the sternum, giving the impression of dextrocardia. As the apex beat could be felt to the left of the sternum, this appearance was thought to be due to a greatly dilated right auricle, probably with all the pulmonary veins emptying into this chamber. Hilar pulsations were normal. Observed in the left anterior oblique view the heart was lobular in shape and the ventricular enlargement appeared to be predominantly right-sided. The shadow of the great vessels was broader in this view than in the anterior-posterior position. There was no enlargement of the left auricle. The liver was on the right side.

The electrocardiogram gave no evidence of dextrocardia; the ventricular complexes in the standard leads were biphasic and of the QS type; the chest leads suggested right ventricular enlargement.

Angiocardiography was performed twice. On the first occasion the injection was made through the left antecubital vein. The diodone entered the heart through two superior venæ cavæ; the one on the right passed directly to the auricle but the left cava drained into the coronary sinus, which in turn, opened into the right auricle (Fig. 1 and 2). The intracardiac circulation was normal and in

FIG. 1.—Angiocardiogram taken at 1½ sec. after beginning of injection.

the later films it could be noted that the pulmonary veins entered the left auricle. The position of the ventricles, however, was distinctly unusual.

The second angiocardiogram was performed through the left external saphenous vein and films were taken in the left oblique position. This proved once again the abnormal position of the ventricles, and the pulmonary artery remained longer opaque than could be expected, making it probable that there was a patent ductus arteriosus.

Cardiac catheterization was performed through the right external saphenous vein. The catheter passed in an unusual way through the right auricle and right ventricle into the pulmonary artery. The oxygen content of the pulmonary artery was 25 per cent higher than the right ventricle, which indicated that the ductus arteriosus was patent.

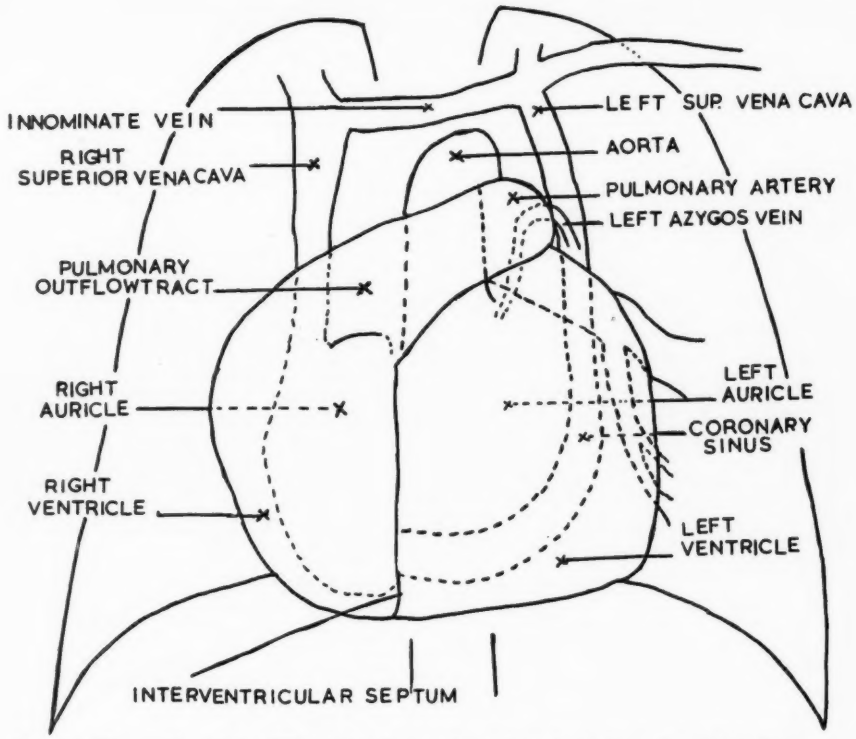

FIG. 2.—The position of the different chambers and vessels as drawn from the angiocardiograms.

Discussion

A case of bilateral superior venæ cavæ associated with incomplete rotation of the heart and patent ductus arteriosus is reported. In the first three months of fœtal life both bilateral superior venæ cavæ (anterior cardinal veins) and the mid-line position of the interventricular and inter-auricular septum are present. This condition has persisted into extra-uterine life. It would appear, therefore, that the developmental arrest, which led to this condition, must have occurred in the third month of pregnancy, but careful interrogation of the mother failed to elicit any cause for the disturbance.

I wish to thank Dr. Clifford G. Parsons for permitting me to publish this case. I am also indebted to Dr. R. Astley and Dr. Helen Wood for their help during the investigations.

REFERENCES

Abbott, M. E. (1927). *Osler's Modern Medicine*, Oxford.
Brandt, W. (1949). *Lehrbuch der Embryologie*, Basel.
Campbell, M., and Hills, T. H. (1950). *Brit. Heart J.*, **12**, 65.
Choake, K. S. (1939). *Anat. Rec.*, **74**, 151.
Dean, J. (1950). *Proc. Royal Soc. Med.*, **18**, 3.
Doll, K (1944). *Act. Path. Microbiol. Scand.*, **21**, 411.
Lam, C. R. (1945). *J. Thor. Surg.*, **14**, 393.
Pro[illegible], M. S. (1943). *Anat. Rec.*, **87**, 99.

A CASE OF ANOMALOUS LEFT CORONARY ARTERY

BY

HUGH FISHER AND OLIVER C. LLOYD

From the University of Bristol

The clinical features of a case in which the left coronary artery arises from the pulmonary artery are so characteristic, that the following example seems worth recording.

Case Record

A girl, aged 5 months, was admitted to hospital on 29/1/50 because of a failure to thrive, associated with enlargement of liver and spleen. She was breast-fed and did well for 8 weeks. As her mother's milk then failed, she was weaned to dried milk but afterwards gained weight only very slowly. There was no vomiting and the motions were normal. She appeared to be full of energy and very active.

On admission, her general condition was good; weight 5·4 kg. (birth weight 3·1 kg.). Rectal temperature 99°. Pulse 120, respirations 30 a minute. Retraction of the costal margin with inspiration. Trachea central. Apex beat in fifth space in anterior axillary line. Heart sounds, normal. Liver smooth and enlarged, 4 cm. below costal margin. Spleen palpable, 1 cm. below costal margin. Blood count: Hb. 10·7 g. per 100 ml. (72%); R.B.C. 3·9 million per cu. mm.

Radioscopy by Dr. R. H. Owen showed the transverse diameter of the heart increased, the enlargement being mainly ventricular, with the right side more prominent than the left.

For the first two days in hospital she took her feeds fairly well though very slowly. She appeared to have colic quite frequently afterwards and vomited small amounts on four occasions. On February 1 her respiratory rate rose to 68 a minute and crepitations could be heard at the base of both lungs. Pulse and temperature were unchanged. A diagnosis of bronchopneumonia was made and she was given penicillin. She appeared to improve after five days and her respiratory rate returned to 30 a minute. She became more difficult with her feeds and on the tenth day she had a sudden collapse during a feed, with pallor, sweating, and tachypnœa. There were rhonchi and crepitations in both lungs. Her temperature rose to 103°, pulse to 140 and respirations to 70 a minute. The heart sounds were "tic-tac." She appeared to improve a little, but the following night collapsed again while being fed, and had severe colic, pallor, sweating, tachypnœa, this time with cyanosis, and required oxygen to revive her. From this time she collapsed after every feed, until her death in an attack on the thirteenth day.

Necropsy findings. (*P.M.* 2788). A slightly wasted infant (4·6 kg., 63 cm. long).

The *heart* weighed 85 g., which is about double the normal weight for this age. This enlargement was mainly due to left ventricular hypertrophy. The *left coronary artery* arose from the left posterior pulmonary sinus. The left atrium showed thickening of the endocardium but the mitral valve was natural. The left ventricle was greatly dilated and the musculature was for the most part hypertrophied, except at the apex, where it was greatly thinned and fibrotic, leading to early aneurysmal dilatation at this point (Fig. 1). The *right coronary artery* had its normal origin from the anterior aortic sinus. The distribution of the coronary vessels over the surface of the heart was such that the greater part of the left lateral and apical surfaces of the ventricles received venous blood from the pulmonary artery. The *liver* and *spleen* showed venous congestion from heart failure. There was also bronchopneumonia.

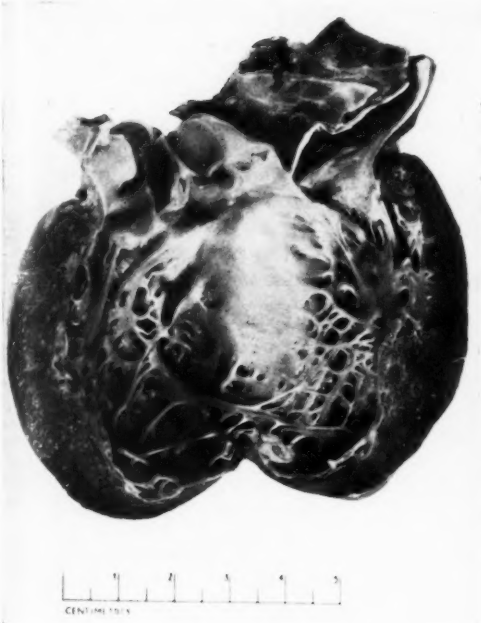

FIG. 1

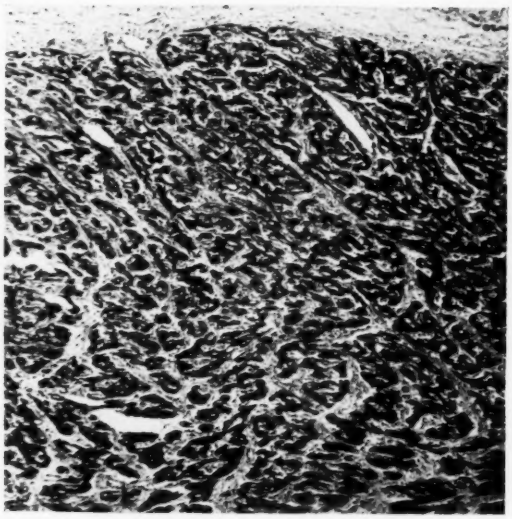

FIG. 2

FIG. 1.—Left ventricle and aortic valves opened to show dilatation and muscular hypertrophy, with fibrotic thinning at apex. The anterior cusp of the mitral valve has been cut through and the right coronary artery is seen originating normally in the anterior aortic sinus.

FIG. 2.—Apex of left ventricle (Masson's trichrome). Diffuse fibrosis. ×70.

Histology. Left atrium: hypertrophy and fibrous thickening of endocardium. Left ventricle: great hypertrophy with a few patches of fibrosis. The tip of the left ventricle showed the greatest degree of fibrosis. The collagen was laid down next to the blood vessels, so that it surrounded each little muscle bundle. Much muscle had atrophied, but the surviving fibres were hypertrophic (Fig. 2). This appearance is quite different from an adult ischæmic fibrosis, where one sees islands of surviving muscle in a sea of fibrous tissue.

Discussion

The origin of the coronary arteries in this case is illustrated in Fig. 3. When the left but not the right coronary artery arises from the pulmonary trunk it produces a group of symptoms and signs that as Bland *et al.* (1933) first pointed out, may allow a diagnosis to be made during life. The electrocardiograph is characteristic: there is inversion of the T waves in all three leads, with no axis deviation and the QRS complexes may be of low amplitude. Venous blood is supplied to the myocardium of the left ventricle at a low pressure, so that the resulting ischæmia is more severe than in cases of cyanotic heart disease, when only the former factor operates. Myocardial fibrosis follows, usually without infarction, producing dilatation of the ventricle and hypertrophy of the surviving muscle. This provides an interesting illustration of the fact that hypertrophy may result from dilatation in the absence of valvular disease or hypertension. Symptoms usually appear at the age of 3 to 4 months which is about the time when, following complete closure of the ductus arteriosus, the systolic pressure of the pulmonary circulation first falls below that of the systemic.

The condition is often fatal by the age of 6 months. Gasul and Loeffler (1949) list 26 cases that have now been reported; all except 5 died in infancy, but the remainder were symptom free and reached adult life. Post mortem, the latter were found to have developed a collateral circulation between the two coronary arteries.

Clinical picture. The most significant symptom is what appears to be severe colic associated with pallor, sweating, and tachypnœa during or after a feed. It is probably equivalent to angina pectoris in an infant. This results in malnutrition. Later, cardiac failure develops and respiratory symptoms become prominent. Many of these cases are mistakenly thought to have bronchopneumonia. The heart progressively increases in size. Hepato-splenomegaly as a result of chronic venous congestion is frequently present. In this case it was the reason for the child's admission for investigation. Cyanosis is only a late sign. Œdema of the extremities may also occur. No murmurs are to be heard on auscultation.

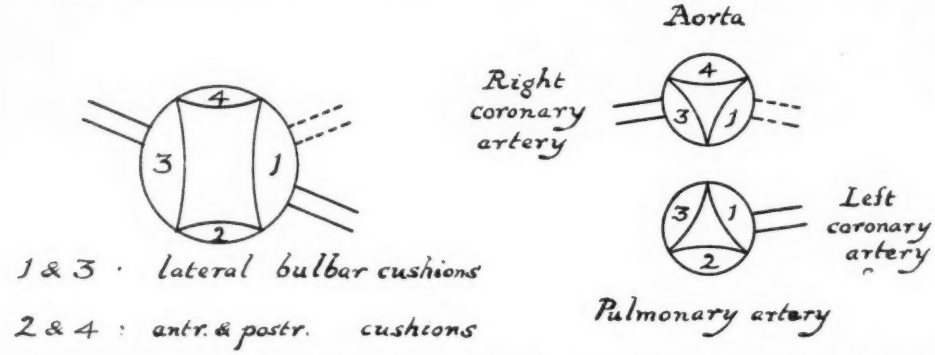

FIG. 3.—Diagram illustrating embryology of anomalous origin of left coronary artery. The diagram on the left shows the origin of the coronary arteries from the truncus arteriosus. The two diagrams on the right show how the development of the spiral septum has produced the aorta and pulmonary artery. The dotted lines show the normal origin of the left coronary artery from the posterior part of the left lateral bulbar cushion.

The diagnosis is confirmed by fluoroscopy and electrocardiography. An X-ray shows the heart to be greatly enlarged, the left ventricle being most prominent. Taussig (1947) mentions that there may be a difference in the force of contraction of the two ventricles. In the left anterior oblique position, the right ventricle anteriorly may be seen to pulsate normally, while the left ventricle posteriorly shows only weak pulsations.

Summary

A case is described of a child dying of cardiac failure due to the anomalous origin of the left coronary artery from the pulmonary artery. The necropsy findings are described.

Our thanks are due to Dr. B. D. Corner for permission to publish this case, to Dr. R. H. Owen for the radiological findings and to Mr. G. H. Rogers for the photographs.

REFERENCES

Bland, E. F., White, P. D., and Garland, J. (1933). *Amer. Heart J.*, **8**, 787.
Gasul, B. M., and Loeffler, E. (1949). *Pædiatrics*, **4**, 498.
Taussig, H. B. (1947). *Congenital Malformations of the Heart.* 1st ed., New York, p. 321.

RHEUMATIC PERICARDITIS IN EARLY CHILDHOOD

BY

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Acute rheumatism occurring under the age of 3 years is uncommon and only three cases of rheumatic pericarditis with effusion appear to have been reported in this age group, the youngest being a child aged 2½ years reported by Ellenberg and Cook (1944). Antell (1935) and Massie and Levine (1939) each report one case, aged 3 years. Killian (1934) mentions seven cases of fœtal pericarditis but considered that syphilis was the more likely cause.

In view of the rarity of recorded cases it is felt that the following two might prove to be of interest.

Case Notes

Case 1. A boy, aged 2½ years, was quite well until July, 1949, when he became rather cross and irritable. During September he was believed to injure his right foot but an X-ray examination at the time disclosed no abnormality. He frequently complained of pain in the right foot during the following weeks. His mother noticed that he became ill-looking, pale, and slightly breathless during the week prior to his admission to hospital in October.

On examination, his face was pale and somewhat puffy. The alæ nasi were moving vigorously. The apex beat was palpable in the fifth left intercostal space just inside the mid-clavicular line. The heart sounds appeared normal. There was a well marked pericardial friction rub down the left border of the sternum. The throat was inflamed but the tonsils did not appear enlarged. Temperature was 100·2° F. and pulse 120. Blood pressure 105/60. Hb 80 per cent (Sahli). Red blood cells 4,480,000 per c.mm., leucocytes 14,600 per c.mm. B.S.R. 47 mm. in the first hour. Urine was normal. Mantoux 1–1000 was negative. X-ray of the chest showed an enlarged cardiac shadow. A culture from a throat swab showed a moderate growth of hæmolytic streptococci; no K.L.B. On the third day following admission the child was still breathless and anxious. The apex beat was not easily localized but appeared to be in the fifth intercostal space outside the mid-clavicular line. The heart sounds were distant and the friction rub had disappeared. The area of cardiac dullness was enlarged to percussion and extended beyond the apex beat. There was an impaired percussion note with diminished air entry at the base of the left lung. A further X-ray showed an enlarged cardiac shadow suggestive of a pericardial effusion.

An electrocardiogram taken on the fourth day following admission showed a sinus tachycardia with inverted T waves in leads III and V2; 6 weeks later, T waves were upright in all leads.

In view of the throat infection on admission the patient received 50,000 units of penicillin 4-hourly for 4 days.

Three weeks later the little boy's condition was greatly improved. Temperature had been normal from the sixth day. The signs of pericarditis had disappeared and radiologically the heart shadow had returned to normal. B.S.R. 23 mm. in the first hour. The Mantoux 1–1000 and 1–100 were again negative.

Two months following admission the child appeared well. Clinically the heart was normal apart from a soft localized systolic murmur at the apex. X-ray examination showed a normal heart shadow. B.S.R. 5 mm. in the first hour.

Six months later, the child was free from symptoms and appeared well. Clinically the heart was not enlarged, the sounds were of good quality and there was a soft apical systolic murmur, which was not conducted.

Case 2. A girl, aged 3 years, became listless, feverish, and refused food. She was seen at intervals by the family doctor until 11 days later he noticed that she had developed a cardiac murmur and advised her admission to hospital.

On examination, the child was flushed and very breathless. The apex beat was in the fifth left intercostal outside the mid-clavicular line. There was a well marked friction rub heard over the base of the heart and a loud systolic apical murmur conducted into the axilla. The area of cardiac dullness was enlarged to percussion beyond the apex beat. There was an impaired percussion note and tubular breathing at the base of the left lung. The throat appeared normal. Temperature was 100° F. and pulse 120. Hb 80 per cent (Sahli). Red blood cells 3,030,000 per c.mm., leucocytes 8200 per c.mm. Urine was normal. Mantoux 1–1000 was negative.

She remained extremely ill during the following ten days. No B.S.R. estimation was done as any attempt was strongly resented. In fact it was only with difficulty that a satisfactory fluid intake was maintained owing to the patient's poor condition and the degree of upset produced by the least interference.

Eight days after admission the friction rub had greatly diminished and a diastolic murmur became audible at the second left intercostal space and was conducted down the sternum. The apical systolic murmur remained unchanged. A chest X-ray showed an enlarged heart shadow with atelectasis of the left lower lobe. The cardiac shadow suggested the presence of a pericardial effusion.

After three weeks there was some improvement. The apex beat was in the fifth intercostal space in the mid-clavicular line. There was no clinical evidence of pericarditis. The apical systolic murmur could be heard over a wide area but the diastolic murmur could not be detected. A further X-ray showed an enlarged cardiac shadow but the left lung field was now clear. The Mantoux 1–1000 and 1–100 was again negative. An electrocardiogram taken on three occasions showed no abnormality.

The patient continued to improve fairly quickly and was much less resentful of interference. The systolic murmur became less audible and after 7 weeks no murmurs could be heard. The apex beat had returned to its normal site. The patient was discharged home after 10 weeks.

Ten months after the onset the child appeared very well. The heart appeared normal apart from a faint localized systolic murmur at the apex.

Comment

Two cases of pericardial effusion due to rheumatism have been described. It is interesting that neither of these presented the usual picture of acute rheumatism with joint pains unless the injury to the foot in Case 1 could be discounted and the symptom regarded as rheumatic in origin. Salicylates were refused by both patients and this was in keeping with the findings of Ellenberg and Cook (1944). In both the presence of signs at the base of the left lung in an acute illness might suggest pneumonia if the cardiac condition was overlooked. Tuberculosis was considered as a possible ætiological factor in both cases but a consistently negative Mantoux reaction, the absence of any pulmonary lesion, and the course of the illness were against this diagnosis. A paracentesis was not carried out as it did not appear justified and the leucocyte count was not suggestive of pus in the pericardium.

References

Antell, L. (1935). *Arch. Pediat.*, **52**, 1.
Ellenberg and Cook (1944), *J. Pediat.*, **24**, 662.
Killian, S. T. (1934). *Amer. J. Dis. Child.*, **61**, 886.
Massie, E., and Levine, S. (1939). *J. Amer. med. Ass.*, **112**, 1219.

INCIPIENT SYMMETRICAL PERIPHERAL GANGRENE COMPLICATING PNEUMONIA

BY

OLE STORSTEIN

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Abrahams (1948) reported a case of incipient symmetrical peripheral gangrene complicating paroxysmal tachycardia. Swan and Henderson (1951) reported two cases of the same condition in myocardial infarction. It may therefore be worth while giving an account of another case of symmetrical peripheral gangrene, apparently provoked by pneumonia. The analytical studies of the gases of the arterial blood and the post-mortem examination may throw some light of the pathogenesis of this condition.

Case Report

S. O., a 58-year-old shop-assistant, was healthy until about October 20, 1948, three weeks before admission, when she started to become breathless. She had to stop and rest repeatedly on her way home after the days work. A couple of days later her fingers began to swell, especially in the morning, the swelling diminishing a little during the day. After a week the fingertips started to get blue, and at the same time the fingers became painful. The pains were constant and resembled tooth-ache, becoming worse while she was at work, packing and delivering cakes and pastries. After some days she therefore had to stop work. She consulted a physician, who gave her something to relieve the pain. At night she slept with her arms above her head, as this position relieved the pain somewhat. Her dyspnœa continued, but she had no pain in her chest and no cough.

On admission to hospital on November 13, 1948, the patient was very obese, her height being 153 cm. and her weight 83 kg. She sat in bed, and was very dyspnœic, with pronounced cyanosis, her cheeks, lips, chest, and back being dark blue in colour. The cyanosis was most pronounced at the fingertips, which were approximately the colour of blue-berries. The fingers were cold and very sensitive to the slightest touch. Her blood pressure was 145/60; the temperature was 39·8° C. and had been 39·7°, two days before admission when it was first taken; the pulse was 120, regular; respiration rate was 40. There was no œdema. Clinically the heart was enlarged to the left, the point of maximum impulse being 11·5 cm. from the mid-line. At the apex a systolic murmur, grade 2, was heard. At the base of the right lung there was dullness to percussion and reduced breath sounds. At both bases there were numerous dry râles. The electrocardiogram was normal with left axis deviation. Chest X-ray then and a week later showed patchy infiltration in both lower lung fields, partly confluent. The examination of the eye-grounds showed shifting calibre of the arteries, arteriovenous nicking, and in the left eye-ground a small area of degeneration.

Measurement of the skin temperature on November 18 gave the following temperatures (room temperature 20° C.): in the palm of the right hand 37·4° C.; on the volar side of the mid-phalanges 36° C.; at the end phalanges: 1st finger, 32·8° C.; 2nd finger, 29·7° C.; 3rd finger 35·5° C. (this finger was not cyanotic); 4th finger 32·2° C.; and 5th finger 34° C. On the left hand the temperature at the cyanotic end-phalanges of the 3rd, 4th and 5th fingers were respectively: 28·2° C., 28·2° C. and 29° C.

There was some leucocytosis, the highest count of white blood corpuscles being 16,000. Sedimentation rate was 35–68 mm. an hour. There was a pronounced hypoproteinæmia: total protein 3·5 g., albumin 2·2, globulin 1·3 g. per 100 ml. The cold agglutination test was negative. Repeated blood-cultures were sterile.

On November 13 the arterial oxygen saturation was found to be 48·9 per cent (oxygen capacity 17·1, oxygen content 8·4 volumes per cent). The patient was treated continuously with oxygen (oro-nasal mask). On November 15 the arterial oxygen saturation was 68·8 per cent in the brachial artery and 69·3 per cent in the femoral artery half an hour after removal of the oxygen mask. Ten minutes after reapplication of the mask the arterial oxygen was fully saturated.

Apart from the oxygen treatment the patient was given sulphadiazine 16 g. and penicillin 1·6 million O.U. The temperature fell slightly, to 38° C., but the patient's general condition had deteriorated, and she died November 24.

Necropsy (Professor Waaler). There was cyanosis of the fingertips of the right hand with incipient gangrene of the 2nd finger. On the left hand there was cyanosis of the 3rd, 4th and 5th fingers, with incipient gangrene of the 3rd.

The lungs were heavy and consolidated in all the lobes, the weight of the right lung being 980 g. and of the left lung 780 g. The hilar lymph nodes were hyperæmic and almost the size of walnuts. The heart weighed 400 g. and showed no hypertrophy of the right ventricle. The spleen weighed 175 g. and was soft.

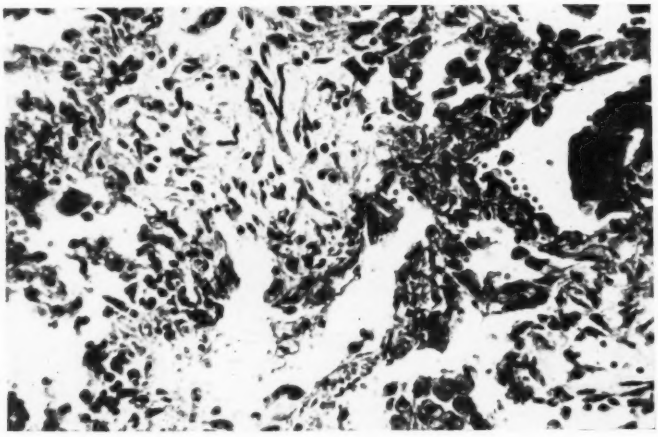

FIG. 1.—Pneumonia in organization; macrophages in the alveoli, proliferation of fibroblasts and blood vessels.

At the microscopic examination of the lungs the alveoli were filled with an exudate of macrophages, some granulocytes and degenerated red blood cells. The alveoli were partly atelectatic. In several places there was abundant proliferation of fibroblasts and blood vessels into the exudate (Fig. 1). In the right upper lobe a thrombus showing incipient organization was found in a small lung vein (Fig. 2).

The artery of the left 3rd finger was slightly thickened, with infiltration of lymphocytes and plasma cells in the adventitia, and moderate cell infiltration in the media. The lumen contained a thrombus in which the structure of the red cells had not quite disintegrated, with incipient organization (Fig. 3).

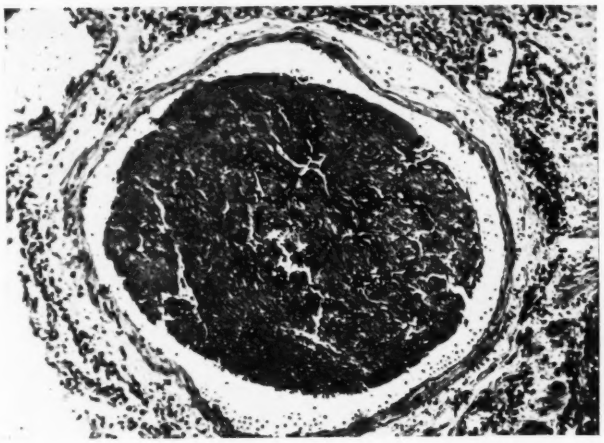

FIG. 2.—Unattached thrombosis in a small lung vein. Destruction of red blood corpuscles, incipient organization.

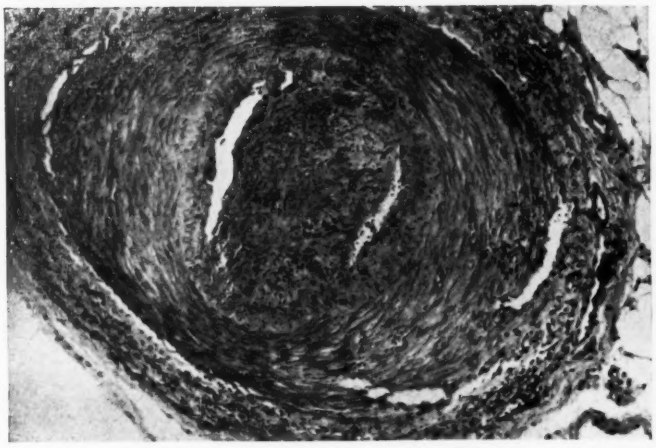

FIG. 3.—Thrombosis in a finger artery. Thickening of the artery wall with infiltrating cells in the adventitia and media; incipient organization of the thrombus.

Discussion

The first point we wish to emphasize is the dyspnœa, which may have been caused by a migrating pneumonia. The stage of development of the pneumonia as revealed by necropsy would tally with the duration of the illness. The evoking agent of the pneumonia was not found, but bacteriological examination of the lungs at necropsy revealed coli bacilli and alpha-hemolytic staphylococci. The evoking agent may have been destroyed by the penicillin therapy or it may have been a virus.

The next point we wish to discuss is the symmetrical peripheral gangrene. The mechanism of this condition has been discussed by various authors, and there are three main possibilities.

Thrombo-embolism. Uhr (1938) has found septic arterial thrombi in gangrene during septicæmia, pneumococci in an artery in a gangrenous toe in a 9-year-old boy with pneumonia. Chatterjee (1940), too, mentions the possibility of the wandering of emboli from the diseased lung to the extremities. The finding in our case of a thrombus in a lung vein may lend support to this view.

Vasospasm, possibly provoking thrombosis. Abrahams as well as Swan and Henderson, following Fishberg (1940), concludes that reflex peripheral vasospasm, evoked by a critical low cardiac output, was responsible in the cases they reported. Chatterjee came to the same conclusion in a case of gangrene of all four extremities in severe pneumonia. This view may also be supported by the finding by Perry and Davie (1939), of symmetrical peripheral gangrene of the lower limbs in congestive hypertensive heart failure.

In some of these cases there is presumably a low cardiac output, but certainly not in all. We did not measure the cardiac output in our case, but in anoxæmia there is usually a high cardiac output (Wiggers, 1949). A very short circulation time in this patient—8 seconds for the first taste to decholin, 17 seconds for the last taste—may indicate a high cardiac output.

Anoxæmia. This point, has not, so far as we know, been discussed in the pathogenesis of this condition, nor has the arterial oxygen saturation been determined in any of the published cases. In cats, v. Euler and Liljestrand (1946) have shown that anoxæmia is a vasoconstricting factor in the lungs. The same reaction of the pulmonary circulation to anoxæmia is found in man (Motley *et al.*, 1947). In the systemic circulation Wiggers supposes local vasoconstriction in some areas to maintain a normal blood pressure in vital organs like the kidney, brain, and coronary circulation. During continued severe anoxæmia this regulation of the systemic blood pressure by local vasoconstriction finally fails, and the blood pressure drops suddenly (Ershler *et al.*, 1943).

In our patient the blood pressure was well maintained until death. It may well be, although we have no proof of it, that local vasoconstriction in the finger arteries, induced by severe anoxæmia, was the initiating factor in the thrombosing process. She was treated continuously with oxygen through an oro-nasal mask, apart from feeding and mouth toilette, for 13 days in all. It may be of interest to note that at necropsy there was no sign of oxygen poisoning (Barach, 1948; Ohlsson, 1947).

Summary

A case of incipient symmetrical peripheral gangrene of the fingers in a case of pneumonia is described. The necropsy revealed that the patient had probably had a migrating pneumonia and that thrombosis in a finger artery had caused the incipient gangrene. Three possible pathogenetic factors in this thrombosis are discussed: (1) embolic spread from the pneumonic lung, (2) vasospasm leading to thrombosis of the artery, and (3) anoxæmia causing vasoconstriction and thrombosis.

References

Abrahams, D. G. (1948). *Brit. Heart J.*, **10,** 191.
Barach, A. L. (1948). *Physiologic Therapy in Respiratory Diseases.* Philadelphia.
Chatterjee, S. C. (1940). *Calcutta med. J.*, **37,** 221.
Ershler, I., Kossmann, C. E., and White, M. S. (1943). *Amer. J. Physiol.*, **138,** 593.
V. Euler, U. S., and Liljestrand, G. (1946). *Acta Physiol. Scand.*, **12,** 301.
Fishberg, A. M. (1940). *Heart Failure.* Philadelphia.
Motley, H. L., Cournand, A., Werkø, L., Himmelstein, A., and Dresdale, D. (1947). *Amer. J. Physiol.*, **150,** 315.
Ohlsson, W. T. L. (1947). *Acta Med. Scand. Suppl.*, 190.
Perry, C. B., and Davie, T. B. (1939). *Brit. med. J.*, **1,** 15.
Swan, W. G. A., and Henderson, C. B. (1951). *Brit. Heart J.*, **13,** 68.
Uhr, J. S. (1938). *Amer. J. Dis. Children*, **56,** 1317.
Wiggers, C. J. (1949). *Physiology in Health and Disease.* Philadelphia.

ABSTRACTS OF CARDIOLOGY

Electrocardiography and Cardiac Physiology. J. S. Robb. *J. appl. Physiol.*, **3**, 1–11, 1950. 5 figs., 10 refs.

Standard and unipolar leads were recorded in normal men and in dogs, certain variations being made in normal electrocardiographic procedure: (1) The connections to the galvanometers were kept constant, whatever lead was being recorded. (2) In recording augmented unipolar leads, one set of electrodes was applied to the extremities nearer the elbow or knee than is usual, and a second set near the wrists and left ankle; these distal electrodes were connected through a resistance of 100,000 ohms to a Wilson central terminal. Amplitude was gained by increasing the degree of amplification rather than by removing one electrode contact. Intracavitary potentials were recorded in dogs.

With this technique it was found, when multiple leads (60 or more) were taken from the thorax, that a line could be drawn round the thorax; from points cephalad to this the records had an initial upstroke, while those from points caudad had an initial downstroke. The amplitude of these initial waves was shown to change in an orderly manner, the greatest positivity being cephalad and to the right and the greatest negativity caudad and to the left. When the galvanometer connections were kept constant aVr was not the reverse of lead I, and aVF leads from the lower part of the thorax had identical polarity. In view of these observations it is suggested that the currently held theory that only depolarization of surface muscle is recorded in the electrocardiogram must be discarded, or alternatively it must be accepted that deep potentials are recorded. It is claimed that the findings recorded can be explained adequately as due to depolarization waves, transmitted along muscle strands and parallel to the direction of its fibres, which are approaching the electrode in one case, and receding from it in the other, thus producing a positive and a negative deflection respectively.

[This closely reasoned paper should be read in its entirety. Provocative rather than convincing, it yet presents data which are not easily reconciled with current orthodox views.] *William A. R. Thomson*

Acute Primary Carditis. I. A. Feder, J. Hoffman, and S. Sugar. *Amer. J. med. Sci.*, **220**, 144–155, Aug., 1950.

Acute primary pericarditis is believed by the authors to be more common than is generally recognized. Five illustrative cases are described. The chief complaint was of substernal or præcordial pain, often during a respiratory infection. Clinical signs of a pericardial effusion and pleural effusion were sometimes found. Serial electrocardiograms showed elevation of the RS–T segment and inversion of the T wave. In some cases the electrocardiographic signs persisted after the symptoms had disappeared. Radiological examination showed a typical change in cardiac silhouette. The condition may recur. No definite ætiological factor has been found and the treatment is symptomatic. The relation of the condition to constrictive pericarditis has not been determined. *H. E. Holling*

After-history of Successfully Treated Cases of Subacute Bacterial Endocarditis. H. Matthew. *Brit. med. J.*, **2**, 436–439, Aug. 19, 1950.

Twenty cases of subacute bacterial endocarditis have been closely followed up for 27 to 63 months after treatment with penicillin. No case relapsed or became reinfected. One patient died. Of the remainder, one developed a hemiplegia, and one congestive heart failure, but the rest are working as hard as before their illness. Four have married and two have borne children without difficulty.

No heart normal in size before treatment became enlarged. In 4 cases the heart increased in size during treatment, but no regression or further enlargement has been noted. One patient has acquired aortic incompetence since infection. No others show auscultatory evidence of fresh valvular damage. Three patients developed paroxysmal auricular fibrillation, one frequent ventricular extrasystoles. In 2 cases of infection of congenitally stenosed pulmonary valves exercise tolerance has now increased. The difficulty of assessing the roles of bacterial and coincident rheumatic infection is stressed. *D. Verel*

Therapeutic Experiences with Subacute Bacterial Endocarditis, with Special Reference to the Failures. D. Littmann and R. S. Schaaf. *New Engl. J. Med.*, **243**, 248–252, Aug. 17, 1950.

Cases of subacute bacterial endocarditis treated at the Massachusetts General and West Roxbury Veterans Administration Hospitals are discussed. Comparison of the cases treated in 1944–46 with those treated in 1947–49 shows that the disease incidence has fallen by almost half, but the condition has become more resistant to treatment by antibiotics. This change is thought to be due to the increasing use of antibiotics for other comparatively trivial ailments, resulting in cure of the undiagnosed cases of endocarditis and increased resistance to antibiotics in the remaining cases.

Not a single instance of bacterial endocarditis superimposed on coarctation of the aorta occurred in this series of 97 cases. Congenitally bicuspid aortic valve was a frequent underlying lesion in fatal cases.

Death was more frequently due to irreversible cardiac, renal, or cerebral changes, than to failure to combat the

infection. This indicates that the infection should be recognized early and adequately treated if the outcome is to be successful. *H. E. Holling*

Can Systolic Expansile Pulsation of the Auricle be Taken as a Criterion of Mitral Incompetence? R. FROMENT, A. GONIN, and L. GALLAVARDIN. *Arch. Mal. Cœur*, **43**, 678–686, Aug., 1950.

The radiological finding of systolic expansion of the left atrium in a patient with suspected mitral disease is usually taken as proof of mitral incompetence. The authors point out that of the cases of mitral disease reported by Lenègre there were 19 which did not show systolic expansion of the left auricle; of these, 4 patients had characteristic murmurs of mitral incompetence. There were 52 with systolic expansion of the left auricle but of these 10 had no systolic murmur and were thought on clinical grounds to have pure mitral stenosis. The authors' doubts appeared to be confirmed by a case of systolic expansion of the left atrium which they record. At necropsy the valves, though stenosed, were completely competent.

They conclude that systolic expansion of the auricle is not pathognomonic of mitral regurgitation but is mostly due to an upward movement of the atrio-ventricular septum during ventricular systole. The sign is not one of mitral incompetence but of mitral disease and consequent dilatation of the left atrium.
H. E. Holling

Myocardial Involvement in Friedreich's Ataxia. J. VARELA DE SEIJAS AGUILAR and J. A. GONZÁLEZ MARTÍNEZ. *Rev. clin. esp.*, **38**, 191–196, Aug. 15, 1950.

The nature of the myocardial involvement in Friedreich's disease is not known exactly but the changes may be of diagnostic value.

The clinical signs are tachycardia, especially paroxysmal, auricular fibrillation, and heart block; there may also be an apical diastolic murmur associated with cardiac dilatation. In their series the authors found an abnormal electrocardiogram in 5 out of 8 cases. In only 2 cases were there clinical signs of heart disease, an apical diastolic murmur with enlargement of the left ventricle. *Paul B. Woolley*

The Syndrome of Cardiopulmonary Schistosomiasis (Cor pulmonale). M. R. KENAWY. *Amer. Heart J.*, **39**, 678–696, May, 1950.

Seven cases of bilharzic cor pulmonale were described. In one of the patients necropsy was performed and the detailed pathological findings recorded. Diagnosis of early cases can be made and confirmed radiologically. The X-ray appearance is that of the well-known " mitral configuration."

The responsible lesions are mainly vascular, consisting of obliterative arteriolitis, produced by the passage of bilharzia ova through the arteriolar wall in an attempt to form extravascular parenchymatous tubercles. Healing of the intimal and medial lesions results in obstruction, which in some arterioles is complete. This is eventually followed by dilatation and atheroma of the main pulmonary artery, and by marked hypertrophy of the right ventricle.

Hæmoptysis was observed in 2 patients in the series.—
Author's summary

Aortic Embolectomy. M. R. EWING. *Brit. J. Surg.*, **38**, 44–51, July, 1950.

In this paper two cases of aortic embolectomy are described in detail.

Both patients were women with rheumatic heart disease and auricular fibrillation, and in both cases the presenting symptom was a sudden feeling of numbness in both legs, with relatively little lower abdominal pain. In both life and limb were saved.

The condition and the technique of operation are discussed. Operation is always worth while, because the result of conservative treatment is usually disastrous either to limb or life. *F. B. Cockett*

Pulmonary Changes due to Cardiac Disease with Special Reference to Hæmosiderosis. A. C. LENDRUM, L. D. W. SCOTT, and S. D. S. PARK. *Quart. J. Med.*, **19**, 249–262, July, 1950.

Hæmosiderotic foci of varying extent were found in the lungs of patients with mitral stenosis only when there was hypertrophy of the right ventricle, foci being strikingly absent when there was concomitant tricuspid stenosis. In a proportion of cases this pulmonary hæmosiderosis can be detected many years before death and is sometimes present in symptomless cases. *W. S. Killpack*

Bernheim's Syndrome Considered in the Light of a Fatal Case. E. B. WILSON and S. L. ZIMMERMAN. *Amer. J. med. Sci.*, **220**, 257–261, Sept., 1950.

A case of anasarca with marked venous congestion but without evidence of pulmonary engorgement is described. Aortic incompetence was present and a chest radiograph showed gross enlargement of the left ventricle, the lung fields being clear. At necropsy the left ventricle was found to be much hypertrophied, measuring 3·5 cm. in diameter. The septum measured 3 cm. across and bulged into the cavity of the right ventricle, reducing this to a slit. The authors suggest that Bernheim's syndrome should be diagnosed in cases of heart disease whenever left-sided failure would be anticipated, both from ætiological considerations and from the presence of enlargement of the left ventricle, and yet signs of systemic venous enlargement far outweigh those of pulmonary congestion. *C. W. C. Bai*

" Medical Sympathectomy " in Hypertension. A Clinical Study of Methonium Compounds. R. TURNER. *Lancet*, **2**, 353–358, Sept. 2, 1950.

The author concludes that the methonium drugs have no place in the routine management of hypertension, though they may be of value in treating certain resistant related symptoms. There is as yet no clear evidence that continuous reduction of blood pressure by drugs

that paralyse the autonomic nervous system will prove beneficial in the long run to hypertensive patients, and it may well prove harmful to some. Even if desirable, such reduction is not easy to achieve with these compounds. *T. Semple*

Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests. M. M. Best and W. S. Coe. *Circulation*, **2**, 344–350, Sept., 1950.

The effect of khellin was tested in 9 cases of ischæmic heart disease. Objective evidence that khellin caused coronary vasodilatation was supplied by means of both the effort test and the anoxæmia test. Electrocardiograms of 4 cases provide convincing evidence that khellin is therapeutically active. Only in 1 of the 9 patients was the condition not improved by the drug. Nausea and vomiting of moderate severity occurred in 3 cases. The dose was 50 mg. orally three times a day for 2 to 4 weeks. *Paul Wood*

One hundred per cent Oxygen in the Treatment of Acute Myocardial Infarction and Severe Angina Pectoris. H. I. Russek, F. D. Regan, and C. F. Naegele. *J. Amer. med. Ass.*, **144**, 373–375, Sept. 30, 1950.

The authors conclude that the administration of 100% oxygen had no influence on myocardial anoxia in patients with acute myocardial infarction or angina pectoris in which blood arterial oxygen saturation was normal. As a therapeutic method for the relief of intractible pain it has no place. There is even evidence that hyperoxygenated blood may interfere with the reactive hyperæmia evoked by myocardial anoxia. This is, however, no contraindication to the routine administration of oxygen whenever other indications for its use in such cases are present. *J. L. Lovibond*

Persistent Truncus Arteriosus. A Clinicopathologic Study. V. Moragues. *Amer. J. clin. Path.*, **20**, 842–853, Sept., 1950.

The post-mortem findings in 4 cases of persistent truncus arteriosus occurring in infants are reported. Three of the cases were of the "partial" type in which there is some evidence of division of the truncus. The fourth case was an example of the "complete" form, in which there is no division of the truncus and the pulmonary arteries arise directly, and independently, from the common arterial trunk. In a valuable discussion of the radiological appearances it is noted that in 2 of these cases the "diagnostic" shelving of the right ventricle in the left anterior oblique view, described by Taussig, was absent. *James W. Brown*

P... Patterns in Acute Myocardial Infarction. J. H. ...hrmann, H. R. Hipp, and H. E. Heyer. *Amer. J. ...fed.*, **9**, 156–163, Aug., 1950.

In 50 well-authenticated cases of myocardial infarction the relation of the duration, location, radiation, and mode of onset of pain to the mortality rate was studied.

The investigators suggest that, if the cases of severe pain and death before the patient is seen by a doctor are disregarded, there does appear to be some relation between the duration of the pain and the gravity of the prognosis; pain of over 24 hours' duration is associated with the highest mortality (39%). In cases in which pain is limited to the thorax the prognosis is worse than when pain radiates to the neck and limbs. It is suggested that in the former cases the infarction is more dangerous, producing a greater degree of shock and therefore a lessened perception of pain.

The authors point out, however, that these relations are by no means constant. *J. B. Wilson*

The Normal Electrical Axis or Left Axis Deviation in Morbus Coeruleus. Study of 29 Cases. Diagnostic Significance. E. Donzelot, M. Durand, C. Metianu, and P. Vlad. *Arch. Mal. Coeur*, **43**, 577–598, July, 1950.

Among 527 patients with congenital heart disease of the cyanotic type treated at the centre for cardiovascular disorders at the Broussais Hospital, Paris, 29 did not show the usually associated right electrical axis deviation. The electrocardiogram in 22 showed left axis deviation, and in the remaining 7 the electrical axis was normal. When left axis deviation is present in a case of congenital heart disease with cyanosis two conditions come to mind immediately: tricuspid atresia and the much rarer condition of coarctation of the aorta of the infantile type (in children after the age of 2 or 3).

A. I. Suchett-Kaye

Electrokymographic Studies of Abnormal Left Ventricular Pulsations. J. B. Schwedel, P. Samet, and P. Mednick. *Amer. Heart J.*, **40**, 410–429, Sept., 1950.

Studies of abnormal left ventricular pulsation in 70 cases of myocardial infarction and in 15 other cases were undertaken by means of electrokymography.

Abnormal paradoxical left ventricular pulsations were detected by cardioscopy in 48, and by electrokymography in 54 cases out of the 70 cases of myocardial infarction. In respect of localization of the infarcted area, there was correlation between electrocardiography and electrokymography in 100% of cases of anterior-wall infarctions only. Paradoxical pulsation of the left ventricle was detected in a number of the patients with left ventricular hypertrophy but no evidence of myocardial infarction. Hence, the authors conclude, "the finding of paradoxical pulsations on the fluoroscope or electrokymogram does not permit one to conclude that myocardial infarction has occurred." *A. I. Suchett-Kaye*

The Diagnosis and Pathogenesis of Obliterative Vascular Disease of the Lower Extremities. A. M. Boyd. *Angiology*, **1**, 373–390, Oct., 1950.

During the course of 3 years more than 1000 patients with defective circulation in the lower limbs were investigated at the Manchester Royal Infirmary. As most of the patients complained of pain, differential diagnosis was required from a number of conditions, including osteoarthritis, foot strain, and meralgia paræsthetica.

Apart from a few cases of traumatic thrombosis, the disabilities were classified as juvenile obliterative arteritis, primary popliteal thrombosis, and senile obliterative arteritis, the first two usually being associated under the general term " thromboangiitis obliterans " or " Buerger's disease."

Despite its name, the last-mentioned condition occurs in a variety of age groups. In diffuse lesions arteriography shows that the main vessels are narrow and irregular; the arterial walls may be calcified. Thrombosis of the popliteal artery occurs in nearly 50% of cases. The localization of the thrombotic area may depend upon repeated injuries caused by movement of the knee joint. On the other hand, the onset of thrombosis may be determined by hypotension due to prolonged rest in bed. Thrombosis of the superficial femoral artery affects about 13% of cases. In this condition the patient experiences claudication in an apparently healthy limb. Although nutritional changes are absent, gangrene of the limb is more likely to result from femoral thrombosis than from popliteal thrombosis. The distal type of senile obliterative arteritis is characterized by the sudden onset of ischæmic changes in the hands and feet, accompanied by transient attacks of gangrene of the superficial tissues.

Juvenile obliterative arteritis begins in the small arteries of the feet and results in gangrene of the lower limbs. Fungus infection of the toes may constitute an important factor in the ætiology of the disease.

A. Garland

Guillaume Harvey: Etude Anatomique du Mouvement du Cœur et du Sang Chez les Animaux. CHARLES LAUBRY, Membre de l'Institut et de l'Academie Nationale de Medicine. G. Doin & Cie. Paris. 1950. Pp. 224. 1,200 Fr.

Harvey's classic has been translated into many tongues, English, Spanish, German, Russian, Danish, and Swedish. This is the first authentic translation into the French language since Charles Richet, 1879. It forms a dignified production, carrying all the authority and enthusiasm of Professor Laubry and reflecting his profound admiration of Harvey, without whom, he suggests, physiology, complex as it has now become, " would be but a dead letter." The facsimile of the full original Latin text is preceded by Laubry's scholarly appreciation of the discovery of the circulation of the blood, which he divides into three periods, Hippocrates to Galen, the Renaissance, and finally Harvey. His translation which follows is faithful to the original, yet free enough in style and modern idiom to be clear and readable.

J. L. Lovibond

Congenital Heart Disease. J. W. BROWN, M.D., F.R.C.P., Physician to the Grimbsy General Hospital, etc. London: Staples Press. Second edition. (Pp. 344; 30*s*.)

This new edition has been partly rewritten. It contains as did the first edition, a full account of the embryology, morphology, and anatomy of congenital diseases of the heart. In spite of the large field covered, and the numerous references to other works, the book is a pleasure to read. The completeness and the full bibliography, make it valuable for reference. The book is attractively printed and the illustrations are excellent.

Dr. Brown still believes that the maladie de Roger is the commonest congenital abnormality of the heart met with in child life. His wide experience, drawn from the study of so many children, makes it likely that his figures are more representative than those of some recent series, which appear to be unduly influenced by selection. Unfortunately, as there is scant reference to the common mild type of pulmonary stenosis, and none to the loud parasternal systolic murmur heard not infrequently in normal children, doubt still remains.

The electrocardiography is inadequate, being limited to the routine limb leads, whilst the value of the second sound in the pulmonary area as an aid to diagnosis receives little comment. In spite of minor blemishes the general excellence of this book is such that it must find a place in the library of all interested in heart disease.

W. O'Brien

Quinidine in Disorders of the Heart. HARRY GOLD, M.D., Professor of Clinical Pharmacology at Cornell University Medical College, etc. Paul B. Hoeber, Inc., N.Y. 1950. Pp. 115. 16*s*.

The dangers of quinidine therapy have, perhaps, been responsible for excessive caution in its use. Indeed, many of the defeats in quinidine therapy, and even some of the disasters, are often due to using too conservative systems of dosage. The author of this excellent monograph points out that the effective dose of quinidine has to be determined for every individual. In arriving at this the patient's co-operation is often called for. There is scope for much wider flexibility in its administration; in one case the drug had been taken in the large dose of 60 grains (4 g.) a day for 14 years with no ill effect. In other cases the therapeutic result is best achieved by prescribing a dosage scheme to produce a pyramidal summation effect. The initial small " test " dose is probably unnecessary. Good reasons are given against the simultaneous use of digitalis and quinidine.

A refreshing book, which deserves to be widely read.

J. L. Lovibond

Nonspecifice Benign Pericarditis. W. B. PORTER, O. CLARK, and R. R. PORTER. *J. Amer. med. Ass.*, 144, 749–753, 1950.

Cases are reviewed and the authors then quote 219 cases of acute pericarditis. Of these, 14 were diagnosed as having non-specific benign pericarditis. It is noteworthy that the possibility of coronary thrombosis was considered in all the cases.

This essentially benign disease with a good immediate and ultimate prognosis must be distinguished from myocardial infarction. In the former a friction rub is present at the beginning of the illness and lasts a week or more; in the latter it occurs 2 or 3 days after the onset of the pain and is typically transient. The pain in the former is intermittent, and may last for 2 or 3 weeks.

Geoffrey McComa

Pulmonary Hæmosiderosis of Cardiac Origin. A. C. LENDRUM. *J. Path. Bact.*, **62**, 555–561, 1950. 14 figs., 20 refs.

The histological changes found in the lungs in hæmosiderosis of cardiac origin are described. The hæmosiderosis which results from prolonged left ventricular failure is indistinguishable from that due to mitral stenosis. These focal accumulations of hæmosiderin are believed to be the end-result of hæmorrhages from the broncho-pulmonary anastomoses in the mucosa of the terminal bronchioles. The hæmorrhages are believed to follow varicose distension of the anastomoses brought about by raised pressure in the pulmonary arteries, the exit side of the anastomoses. In mitral cases the increase is absolute and persistent; in cases with remittent left ventricular failure there are periodic falls in the bronchial-arterial pressure. From the accumulations of siderophages in the group of alveoli which constitutes the focus, soluble iron reaches the adjacent stroma and there produces damage followed by reactive changes. These in turn, by lymphatic obstruction, tend to perpetuate the accumulation and so accelerate the vicious circle. [Author's summary.]

Angina Pectoris: a Clinical Study with Special Reference to Neurosurgical Treatment. I. LINDGREN. *Acta med. scand.*, **138**, Suppl. 243, 1–203, 1950.

This monograph records the author's experience with cervico-thoracic ganglionectomy, consisting of removal of the stellate ganglion and section of the 2nd, 3rd, and often the 4th thoracic ganglia. A group of 105 patients were operated upon, and a control group of 88 patients with similar symptoms and signs were observed.

Of the 105 patients, 11 died following operation. The mortality rate within 2 years of admission was shown by statistical analysis to be no greater in the operated group than in the control group. The majority of the patients still alive have been followed up for more than 3 years. Definite relief of pain was obtained in 52% of the patients surviving the operation, and some relief in a further 11%, in whom the effect was difficult to evaluate because of progressive cardiac decompensation or other post-operative developments.

The author concludes that the operation should be reserved for a group of patients who, after an adequate period of observation cannot be controlled effectively on a medical regime. The operation is contraindicated by a history of myocardial infarction followed by a permanent drop in blood pressure, by cardiographic changes indicating severe myocardial damage combined with cardiac enlargement, and by the presence of moderate or marked cardiac insufficiency. *D. W. C. Northfield*

The Significance of Q_{AVF} in the Diagnosis of Posterior Infarction. P. N. G. YU and T. M. BLAKE. *Amer. Heart J.*, **40**, 545–553, Oct., 1950.

In view of controversial opinion concerning the clinical value of the unipolar limb leads in the diagnosis of posterior infarction in cases in which a large Q_3 is the only abnormality in the standard-lead electrocardiogram, a comparative and critical study of Q_2, Q_3, and Q_{AVF} was undertaken in 109 cases in which Q_3 was at least 25% of R_3.

It is concluded that the mere presence of a deep Q_3, with or without an inverted T_2, is not a reliable diagnostic sign of posterior myocardial infarction, and that while the finding of a significant Q_2 is definitely helpful in the diagnosis, its absence does not rule out the possibility of a posterior wall lesion; but that the use of the unipolar leg lead can be of real help in the differentiation between the normal and abnormal Q_3 and thus in establishing or excluding the diagnosis of posterior wall infarction.

A. I. Suchett-Kaye

Diet, Serum Cholesterol and Coronary Artery Disease. M. M. GERTLER, W. M. GARN, and P. D. WHITE. *Circulation*, **2**, 696–704, Nov., 1950.

The dietary history of 139 healthy males and of 90 who had suffered myocardial infarction before the age of 40 was investigated. There was no significant difference in the amount of cholesterol contained in the diets of the two groups, nor did the level of cholesterol in the serum appear to be related to the dietary intake. Judging by this study there appears to be nothing to be gained by restricting the intake of cholesterol-containing foods by patients with coronary artery disease.

H. E. Holling

Recent History of Coronary Disease. J. N. MORRIS. *Lancet*, **1**, 1–7 and 69–73, Jan. 6 and 13, 1951.

In England and Wales the number of deaths from coronary heart disease doubled between 1938 and 1948. This might be due to the substitution of "coronary thrombosis" for "myocarditis" in the certificates, but the number of deaths from rupture of the heart found at coroner's inquests more than doubled during the same period. Also the number of recent infarcts found at necropsy at the London Hospital increased seven-fold between the period 1907 to 1914 and that of 1944 to 1948, the greatest increase being from 1916 to 1919, at a time when coronary occlusion was not diagnosed clinically.

The incidence of severe coronary atheroma, however, has decreased. Examination of the necropsy records at the London Hospital shows that there was less advanced atheroma, as measured by calcification of the arteries, in 1944 to 1949 compared with the years 1908 to 1913. The decrease took place mainly during the two war periods and may be ascribed to the rationing of fats.

The problem of why coronary heart disease should increase while atheroma is decreasing is discussed. It seems that while atheroma provides the basis for coronary occlusion, there are precipitating factors affecting the coagulability of the blood. It may also be that calcification of the artery represents a stage of healing, and that subintimal hæmorrhages, possibly with concomitant spasm, are more likely in the earlier stages. In conjunction with the unknown precipitating factors this might account for the tendency in recent years for coronary occlusion to occur in younger age groups.

This paper establishes the fact that in spite of a decreasing incidence of calcified coronary arteries,

myocardial infarction has increased in the last 40 years much more than can be accounted for by the ageing of the population. *C. W. C. Bain*

Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Diseases. A. COURNAND. *Circulation*, **2**, 641–657, Nov., 1950.

The author reviews the additions made in the past few years to our knowledge of the pulmonary circulation and reports certain personal observations. In 10 normal people the range of pressure was found to be: pulmonary artery, systolic 22±2·9 mm., diastolic 8±1·7 mm., mean 13±2·3 mm. Hg; pulmonary capillary pressure 5 mm. Pressure-pulse tracings from the pulmonary capillaries show two distinct positive waves, one of which is thought to be the forwardly transmitted pulmonary systolic pulse, the other the backwardly transmitted left atrial pulse. The latter disappears in auricular fibrillation.

In left ventricular failure there is a rise in the filling pressure of the left ventricle which is transmitted back through the lungs and results in an increased pulmonary arterial pressure. In diseases of the lung restriction of the pulmonary vascular bed results in a rise of pulmonary arterial pressure, particularly under conditions such as exercise when the blood flow is increased. In chronic pulmonary emphysema the elevation of pulmonary arterial pressure shows some relationship to the degree of arterial oxygen saturation. Chronic anoxia due to lung disease leads to an increase in blood volume, polycythæmia, and in increase in cardiac output. These changes put an increased strain on the right heart, which hypertrophies and then fails. In 4 cases of emphysema of varying severity it was found that the more severely affected cases showed a smaller increase in cardiac output on exercise and a greater increase in pulmonary arterial pressure than the milder ones. In chronic lung disease therapy should be directed towards overcoming infection with antibiotics, and the relief of bronchiolar obstruction by the reduction of bronchial secretion and the use of atomized bronchodilators. *H. E. Holling*

Auricular Flutter Studied in Direct Leads from the Human Heart. F. M. GROEDEL and M. MILLER. *J. appl. Physiol.*, **3**, 183–188, Oct., 1950.

A patient with mitral stenosis and impure auricular flutter was subjected to mitral commissurotomy. The opportunity was utilized to explore electrocardiographically the exposed left auricle. The results obtained suggested that poly-focal stimulation of the left auricle was responsible for the rhythm. *Paul Wood*

Procaine Amide (Pronestyl) in the Treatment of Disorders of Cardiac Rhythm. Preliminary Report. J. M. KINSman, H. L. CLAY, W. S. COE, and M. M. BEST. *J. Kentucky med. Ass.*, **48**, 509–511, Nov., 1950.

The effect upon various arrhythmias of procaine amide, given intravenously in doses ranging from 200 mg. to 2000 mg., was investigated in 34 patients. Ventricular ectopic beats were abolished in 10 out of 11 cases, paroxysmal ventricular tachycardia in 2, and auricular extrasystoles in 3 out of 4 patients. No effect was seen in persistent auricular fibrillation and flutter. Side-effects included transient flushing, fall of blood pressure, and occurrence or aggravation of bundle branch block. Further studies, including oral administration, of this drug are in progress. *A. Schott*

Apical Diastolic Murmurs in Patent Ductus Arteriosus. A. RAVIN and W. DARLEY. *Ann. intern. Med.*, **33**, 903–914, Oct., 1950.

At the University of Colorado, the authors studied the heart sounds in 21 established cases of patent ductus arteriosus. In 9 cases apical diastolic murmurs similar to those of mitral stenosis were heard. In several of these cases operative correction of the defect abolished the murmur, and in one case of operative death the absence of coincident mitral stenosis was confirmed at necropsy. It is suggested that the murmur is produced by what is in effect a functional mitral stenosis: although the absolute size of the mitral ring is normal, its size relative to the ventricular capacity and the rate of blood flow is reduced owing to the effect of the shunt between the aorta and the pulmonary artery.

T. A. A. Hunter

Pulmonary Arteriovenous Aneurysm. G. E. LINDSKOG, A. LIEBOW, H. KAUSEL, and A. JANZEN. *Ann. Surg.*, **132**, 591–610, Oct., 1950.

The essential features of the fully developed case of pulmonary arteriovenous aneurysm are cyanosis and clubbing, a clinically normal heart, and a radiological shadow in the lung fields. Epistaxis and hæmoptysis are frequent. Cases do occur, however, in which symptoms are absent, or appear rather abruptly in adult life. In half the cases multiple spidery telangiectases or discrete nodular hæmangiomata are present in the skin or mucous membranes. A continuous murmur with systolic accentuation is often heard over the "tumour." The essential radiological features consist of a saccular, cirsoid, or racemose, clearly defined shadow in the lung fields combined with enlargement of the related vascular shadows. Angiocardiography shows early opacification, and is particularly valuable in demonstrating multiple lesions.

Treatment consists of removal whenever this is practicable, even in symptomless cases, symptoms tending to develop at a later date if such cases are left untreated. Multiplicity of lesions is the chief drawback in carrying out surgical removal. *W. P. Cleland*

Dilatation of the Aorta in Arachnodactyly. [In English]. G. A. LINDEBOOM and E. R. WESTERVELD-BRANDON. *Cardiologia*, **17**, 217–222, 1950. 6 figs., 14 refs.

The incidence of dissecting aneurysm and aneurysmal dilatation of the aorta in reported cases of arachnodactyly is reviewed. Among 13 patients attending an ophthalmic clinic, radiological evidence of enlargement of the aorta was found in 5 cases, with clinical evidence of aortic incompetence in one. One other patient had a congenital heart lesion. *D. Verel*